Chronic Obstructive Pulmonary Disease in challenging environments

A study of risk factors in India and advanced disease management in the United Kingdom

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctorate of Medicine by Dr Biswajit Chakrabarti

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Dedication

I dedicate this thesis to my wife Satarupa and daughter Zara for all their love and support throughout the years. Without them, this work would not have been possible.

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Publications arising from this thesis

Peer reviewed Papers

- **Chakrabarti B, Angus R M, Agarwal S, Lane S, Calverley P M A. Hyperglycaemia as a predictor of outcome during Non-Invasive Ventilation for COPD exacerbations complicated by decompensated ventilatory failure Thorax 2009;64:857–62** (This paper describes the study discussed in Chapter 2 of this thesis; also this was the subject of an Editorial in the same issue)
- **Chakrabarti B, Sulaiman M I, Davies L, Calverley P M A, Warburton C J, Angus R M. A Study of Patient Attitudes in the United Kingdom towards Ventilatory Support in Chronic Obstructive Pulmonary Disease Journal Of Palliative Medicine 2009; 12: 1029-35** (This paper describes the study discussed in Chapter 3 of this thesis)
- **Chakrabarti B, Purkait S, Gun P, Moore VC, Choudhuri S, Zaman MJ, Warburton CJ, Calverley PM, Mukherjee R. Chronic airflow limitation in a rural Indian population: etiology and relationship to body mass index. Int J Chron Obstruct Pulmon Dis. 2011; 6: 543–549** (This paper describes the study discussed in Chapter 4 of this thesis)

A copy of each listed peer reviewed paper is attached in the "Appendices" section

Oral/Spoken Presentations resulting from this thesis

Chapter 2

- **Arterial blood gas changes and failure of acute Non Invasive Ventilation: A prospective analysis (B Chakrabarti, S Agarwal, P M A Calverley, R M Angus).** ERS Annual Congress oral presentation, September 2007

- **A prospective cohort study of variables predicting outcome during Non-Invasive Ventilation for Acute Hypercapnic Respiratory Failure (B Chakrabarti, S Agarwal, R M Angus, P M A Calverley).** BTS oral presentation, December 2007

Chapter 3

- **A study of Non-Invasive Ventilatory Support in COPD & relationship to health status (M I Sulaiman, B Chakrabarti, C J Warburton, L Davies, R M Angus)** British Thoracic Society Winter meeting 2004.

- **Functional status is associated with willingness to undergo invasive mechanical ventilation in COPD (B Chakrabarti, M I Sulaiman, C J Warburton, L Davies, P M A Calverley, R M Angus)** ERS Annual Congress oral presentation, September 2007

Poster Discussions resulting from this thesis

- **A study of Invasive Ventilation in COPD (M I Sulaiman, B Chakrabarti, C J Warburton, L Davies, R M Angus)** Abstract & poster discussion at the British Thoracic Society Winter meeting 2004

- **Setting a ceiling of treatment during acute exacerbations of COPD; A study of patient attitudes and relationship to clinical variables (B Chakrabarti, M I Sulaiman, C J Warburton, L Davies, R M Angus)** Abstract & poster presentation; American Thoracic Society conference May 2005

- **Elevated blood glucose and the outcome of ventilatory failure due to COPD exacerbations: A prospective cohort study (B Chakrabarti, R M Angus, S Agarwal, S Lane, P M A Calverley)** Abstract and Poster presentation; American Thoracic Society Annual Congress May 2008

- **Feasibility of performing valid spirometry in rural India: preliminary results from a population study assessing the prevalence of COPD (R Mukherjee, V C Moore, S Purkait, P Goon, C J Warburton, B Chakrabarti, P M A Calverley). Abstract and Poster presentation; British Thoracic Society Winter meeting 2010**

Review Articles published by the author on the subject of this thesis

- Chakrabarti B, Angus RM; Ventilatory failure on the Acute Take. Clin Med 2005;5:630–634
- Chakrabarti B, Calverley P M A; Management of Acute Ventilatory failure. Postgrad Med J 2006;82:438-445
- Chandramouli S, Molyneux V, Angus R M, Calverley P M A, Chakrabarti B. Insights into COPD patients' attitudes on ventilatory support; Current Opinion in Pulmonary Medicine 2011; 17:98 –102

Prizes resulting from this thesis

North West Thoracic Society 2004 SPR presentation prize winner Presentation on "Study of patient attitudes towards ventilatory support in COPD" won the annual SPR prize for the North West Thoracic Society. This comprised a travel grant sponsored by the British Lung Foundation.

Contributors to this thesis:

Chapter 2: PMAC, RMA and myself conceived the study. I designed the study and was the principal investigator. I undertook data collection along with SA. SL provided the statistical input. I analysed the data and wrote the manuscript.

Chapter 3: Myself, RMA, MIS, LD and CJW conceived the study. I designed the study along with RMA, LD and CJW. I was the principal investigator and undertook data collection and statistical analysis. I analysed the data and wrote the manuscript.

Chapter 4: Myself, RM, PMAC conceived the study. I designed the study along with PMAC, RM, VM and PG. I was the principal investigator and undertook data collection and statistical analysis. I analysed the data and wrote the manuscript.

Chronic Obstructive Pulmonary Disease in challenging environments

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Dr Biswajit Chakrabarti

Abstract

Background: Globally, Chronic Obstructive Pulmonary Disease (COPD) constitutes a significant healthcare burden. In the developed world setting of a large urban hospital, this thesis defines which bedside variables recorded at baseline best predicts outcome from Non Invasive Ventilation (NIV) in the acute setting focusing on the presence of hyperglycaemia. Furthermore, whilst informed patient choice is central to modern clinical care, little is known about how COPD patients respond to information regarding complex therapies. This thesis explores COPD patient attitudes towards Ventilatory support and Advanced Directives of Care (ADCs). In contrast, in the developing world, the thesis aimed to better understand risk factors associated with the finding of airflow obstruction with emphasis on low Body Mass Index (BMI).

Methods: In the developed world, patients with COPD receiving NIV acutely were studied prospectively with random blood glucose levels measured before NIV administration. Secondly, a standardized 5-stage interview process was used to explore attitudes towards Ventilatory Support in 50 stable COPD patients. In the developing world study, patients greater than 35 years of age attending a rural clinic in India underwent evaluation by structured questionnaire measurement of BMI and Spirometry.

Results: Regarding predictive factors for NIV, 88 patients met study inclusion criteria, with NIV successful in 90%. Following multivariate logistic regression, baseline respiratory rate (RR), random glucose ⩾7 mmol/l and admission APACHE II (Acute Physiology and Chronic Health Evaluation II) score were predictive of outcome. The combination of RR <30 breaths/min and glucose <7 mmol/l increased prediction of NIV success to 97% whilst use of all three factors was 100% predictive. When taking COPD attitudes towards Ventilatory Support, 86% found demonstration of NIV helpful in decision making compared to 24% with the photographic aid ($p<0.001$). Patients willing to receive IMV were younger and had a better functional status. Only 34% had heard of advanced directives of care, none had ever issued one but 48% expressed interest in doing so following explanation of ADCs. In a rural Indian setting, factors associated with airflow obstruction were: increasing age, smoking history, male gender, low BMI and occupation. AFO was observed in 27% of subjects with a BMI<18.5 kg/m2 falling to 13% with BMI≥18.5 kg/m2 ($p=0.013$).

Conclusions: In the developed world, hyperglycaemia upon presentation, baseline respiratory rate and high APACHE II score were associated with a poor outcome from NIV. Combining these variables increases predictive accuracy potentially aiding risk stratification. COPD patients find demonstration of NIV most useful in an out-patient setting with worsening functional status along with advanced age being associated with reduced willingness to receive invasive ventilatory support. Awareness of ADCs was found to be low. In a rural Indian setting, the finding of airflow obstruction was related to advancing age, smoking history, male gender, reduced BMI and occupation. Our data suggests a mechanistic relationship between low body weight, smoking tobacco and development of airflow obstruction.

CHAPTER 1: OVERVIEW OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1.1 Definition of Chronic Obstructive Pulmonary Disease

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) group define COPD as a condition characterised by persistent airflow limitation which is usually progressive and associated with an enhanced chronic inflammatory response of the airways and lungs to noxious particles and gases (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Revised Version). The agents inhaled by susceptible individuals often include cigarette smoke and biomass fuels thus resulting in an exaggerated and abnormal inflammatory response in the lungs and beyond resulting in the clinical manifestations of COPD. Other "inhaled" agents cited in the development of COPD include organic or inorganic dust matter and marijuana hence underpinning the view that COPD may also be a condition affecting those who have not smoked tobacco (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Revised Version). This chapter provides an overview of the diagnosis, pathophysiology and epidemiology of COPD from a global perspective and particularly focuses on India where one of the studies described in this thesis was conducted.

1.2 Chronic Obstructive Pulmonary Disease: Diagnosis and classification of severity

The diagnosis of COPD relies on the presence of airflow obstruction/limitation when diagnosed on spirometry alongside a compatible clinical presentation (Global Strategy for the

Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Revised Version). The clinical context implies that the patient has symptoms compatible with a diagnosis of COPD such as shortness of breath, cough and sputum production alongside exposures which put the patient at increased risk of having COPD such as inhaling tobacco or biomass fuel smoke or having a family history of COPD.

Using the GOLD criteria, airflow obstruction is diagnosed using simple spirometry as a post bronchodilator FEV1/FVC ratio <0.7. Following the diagnosis of COPD using the FEV1/FVC ratio, the disease severity according to spirometry is classified according to the degree of FEV1 impairment against the predicted value for the patient (see table 1).

Table 1: Classification of severity of COPD

GOLD stage	Spirometry (post bronchodilator)
Mild	**FEV1/FVC<0.7** **FEV1≥80% predicted**
Moderate	**FEV1/FVC<0.7** **FEV1 50% TO 79% predicted**
Severe	**FEV1/FVC<0.7** **FEV1 30 TO 49% predicted**
Very Severe	**FEV1/FVC<0.7** **FEV1 <30% predicted** **or** **FEV1<50% predicted but with chronic respiratory failure**

There is debate as to what constitutes the most optimal spirometry criteria to make the diagnosis of COPD. The GOLD criterion to diagnose COPD relies on the presence of persistent airflow obstruction i.e. post bronchodilator FEV1/FVC ratio less than 0.7. However, there are those who argue that relying on this classification has the potential to misdiagnose healthy elderly patients as having COPD (Enright et al 2008). This is due to the fact that there has been shown to be a natural decline in the FEV1/FVC ratio with age in certain individuals who have never smoked and are otherwise asymptomatic due to the loss of lung elastic recoil which promotes the collapse of airways during expiration (Hardie et al 2002). It has been suggested that using the Lower Limit of Normal (LLN) for FEV1/FVC ratio (i.e. bottom 5% of a healthy non-smoking population) will avoid such misclassification. Nonetheless, despite having its critics, using the GOLD classification system offers clinicians practising in diverse settings a pragmatic methodology to diagnose, classify and foster further research into COPD (Calverley et al 2004). Furthermore, data exists showing that in patients over the age of 65, those who had an FEV1/FVC ratio<0.7 but above the LLN had an increased risk of death and healthcare utilisation when compared to those over 65 with normal lung function thus supporting the use of the GOLD classification system (Mannino et al 2007).

1.3 The pathophysiology of Chronic Obstructive Pulmonary Disease

The manifestations of COPD depend on the extent to which the different components of the respiratory system are affected e.g. the lung parenchyma, small airways etc. (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Revised Guidelines

2011). The pathophysiology of COPD and the effects seen in different parts of the respiratory system are described below:

1.3.1 The major conducting airways: Mucous gland hypertrophy is often a feature in the larger airways of COPD patients resulting in the "hypersecretion" and consequent expectoration of excess mucus. Pathological changes to the large airways include hyperplasia of the mucous producing goblet cells, thickening of the subepithelial basement membrane and fibrosis of the bronchial walls (Fischer et al 2011). Clinically this manifests as the syndrome of "chronic bronchitis" i.e. a chronic productive cough lasting more than 3 months in each of 2 successive years in a patient where other causes of a chronic cough have been excluded (Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society 1995). The term "chronic bronchitis" has been used as a surrogate for the presence of airflow obstruction in smokers in some studies as described in later sections. However, whilst conflicting evidence exists in the literature as to how relevant the presence of chronic bronchitis in an individual is to the development of obstructive spirometry, it has been shown in large epidemiological studies to influence the rate of decline in FEV1 in those individuals who already carry an established diagnosis of COPD and may represents an adverse prognostic marker in the outcome of such patients (Lange et al 1990; Vestbo et al 1996).

1.3.2 The lung periphery and small airways: The term "emphysema" is used to define a destructive process where there is an abnormal enlargement of the airspaces which lie distal to the terminal bronchioles accompanied by destruction of their walls in the absence of fibrosis. Patients with similar values in terms of FEV1 and GOLD staging of COPD may have very different degrees of

emphysema when imaged (Makita et al 2007). The term "Centrilobular" emphysema is most commonly seen in cigarette smokers affecting the lobules around the central respiratory bronchioles and is seen predominantly in the upper lung zones whereas "Panlobular" emphysema affects the whole secondary lobule and is often seen in the lower lung zones and is the most common category of emphysema in cases of alpha-1 antitrypsin deficiency . (Leopold et al 1957; Saetta et al 1994). Paraseptal emphysema is the least common form and involves the most distal part of the lung periphery and is responsible for the formation of bullae. The destructive process affecting the lung parenchyma also result in a loss of alveolar attachments i.e. damage to the "scaffolding" of the small airways. The consequence of these parenchymal changes means that there is a reduced driving pressure when gas is being expelled from the alveolus to the larger conducting airways when a COPD patient breathes out due to the loss of lung elastic recoil i.e. the ability of the lung to deflate back down from being inflated at inspiration. This reduced driving pressure causes a reduction of positive pressure downstream from the alveolus. Thus, the "equal pressure point" where alveolar pressure equals the pleural pressure on the "other side of the wall" actually occurs in the peripheral airways rather than in the central airways where there is no supporting cartilage which results in peripheral airway collapse and a limitation of expiratory flow i.e. pushing air with greater driving force from the alveolus at this point will not result in this air traversing the collapsed small airways. The trapped air which cannot be expelled during expiration results in "hyperinflation" and also creates a positive pressure in the alveolus at the end of expiration (so called "Intrinsic PEEP") which has to be overcome in order to generate a negative pressure in order to draw fresh air into the lungs during inspiration thus increasing the work

of breathing further. In addition, inflammation and obstruction to the small airways i.e. bronchiolitis may also be observed in COPD patients (Fischer et al 2011). Also relevant is the "protease-antiprotease" theory which describes an imbalance which occurs in COPD resulting in an unregulated activity of antiprotease enzymes (Churg et al 2005). This unregulated antiprotease activity results in destruction of the extracellular matrix in the lung parenchyma comprised of collagen and elastin through increased production and up regulation of naturally occurring protease enzymes matrix metalloproteinases (MMPs) via the effect of tobacco smoke on alveolar macrophages (Chakrabarti et al 2007). One example of this is seen in cases of Alpha 1 antitrypsin defiency where defiency of the antiprotease alpha-1-antitrypsin results in unregulated activity of the proteolytic enzyme neutrophil elastase resulting in the development of COPD (Stoller et al 2012).

1.3.3 **The pulmonary vasculature:** The presence of alveolar hypoxia secondary to the parenchymal lung damage in COPD results in the phenomenon known as "hypoxic pulmonary vasoconstriction" aiming to divert blood flow from the areas of greater lung damage where the potential for adequate gas exchange is less to those better ventilated lung units (Bradford J, Dean H. J 1894). Structural changes in the peripheral pulmonary vessels resulting in a thickening of all the vessel wall layers (i.e. the intima, media and adventitia) have been described even in cases of relatively mild COPD (Wright et al 1983). This has also been associated with an inflammation mainly involving CD8+ lymphocytes affecting the more muscular pulmonary arteries which may be due to the direct effect of toxins present in cigarette smoke (Peinado et al 1999). The role of endothelial dysfunction in the pathogenesis of pulmonary hypertension in COPD has also been highlighted. The

production of Nitric Oxide (NO) results in dilation of the pulmonary vasculature whilst mediators such as Endothelin 1 (ET-1) result in vasoconstriction. In COPD patients with pulmonary hypertension, a reduced synthesis of NO has been described as well as increased production of ET-1 (Dinh-Xuan et al 1991; Giaid et al 1993). The end result of the changes described above is an increase in Pulmonary Vascular Resistance by up to 300% (Moudgil et al 2005) and an elevation in Pulmonary Artery Pressure (PAP) causing an increase in right ventricular overload and the clinical features of Right Heart Failure so called "Cor Pulmonale." Pulmonary Hypertension has been defined as a PAP greater than 25mmHg at rest (Galie et al 2009). The presence of pulmonary hypertension portends a worse prognosis in COPD, impacting more than age or FEV1. For example, a study of 84 COPD patients, where the PAP was measured using Right Heart Catheterization, reported a 5 year survival of 36.3% in COPD patients with a mean PAP greater than 25mmHg compared to 62.2% in the group where the mean PAP was 25mmHg or less (Oswald-Mammosser et al 1995). The presence of pulmonary hypertension has also been shown to convey greater functional impairment in COPD patients with one study reporting shorter 6 minute walk distances with a 5mmHg increase in PAP being associated with a 11 metre fall in 6 minute walk distance (Sims et al 2009). Finally, recent evidence indicates that in patients presenting with acute exacerbations of COPD complicated by respiratory acidosis requiring Non Invasive Ventilation, the presence of severe pulmonary hypertension (PA systolic pressure of 55mmHg or greater) showed less marked improvement in blood gas parameters with Non Invasive Ventilation (Parola et al 2012).

1.4 The epidemiology and global burden of Chronic Obstructive Pulmonary Disease

In 2001, Chronic Obstructive Pulmonary Disease (COPD) was estimated as being the 5th leading cause of death in high income countries and the 6th leading cause of death in low or middle income countries (*Lopez AD et al. Global burden of disease and risk factors. Washington: The World Bank, 2006*). However, by 2020, COPD is expected to rise to become the 3rd leading cause of death and morbidity globally (Murray et al 1997). This is highlighted by data from the United States showing that whilst death rates from coronary artery disease and stroke had fallen by 59 and 64% respectively between 1965 and 1998, death rates due to COPD were seen to rise by 163% over the same period (Chapman et al 2006; Pawels et al 2001).

The prevalence of COPD in the Western world has been charted through large scale epidemiological studies. In the United States, The National Center for Health Statistics conducted the First National Health and Nutrition Examination Survey (NHANES I) recruiting 5542 subjects between 1971 and 1975. Questionnaire data encompassing respiratory symptoms, smoking history, pulmonary function and Body Mass Index (BMI) were gathered and here, 8.8% of subjects were classified as having either moderate or severe COPD. More recently, the Burden of Obstructive Lung Disease (BOLD) study aimed to map COPD prevalence globally and enrolled 9425 adult subjects over the age of 40 from sites in 12 countries (Buist et al 2007). The sites studied included mostly industrialised developed nations such as the United States, Canada and Australia but also included sites in China and the Philippines. All subjects completed questionnaires and underwent post bronchodilator spirometry. The overall prevalence of COPD at GOLD stage 2 was reported as 10.1% (11.8% for men; 8.5% for women). The highest prevalence of COPD at Gold Stage 2 or above was seen in the Cape Town site in South Africa where 22.2% of males and 16.7% of females studied were diagnosed whilst a figure of 18.8% of males and 6.8% of females was reported

at the Philippines site. These data contrast to a prevalence of 8.5% in males from the Icelandic site and 12.7% in males from the US site. Advancing age was associated with an increased prevalence of COPD with an odds ratio of 2 per additional 10 years. Several years before the BOLD study, the PLATINO study reported COPD prevalence in 5229 subjects across 5 Latin American cities (Sao Paolo, Santiago, Caracas, Montevideo and Mexico City) defining COPD according to GOLD criteria in adults aged 40 years or older (Menezes et al 2005). Subjects were interviewed, underwent assessment of BMI and spirometry. The highest prevalence was noted in Montevideo, Uruguay at 20% and the lowest in Mexico City at 7.8%. Such data were broadly consistent with earlier studies such as the multicentre Epidemiological study of chronic obstructive pulmonary disease in Spain (IBERPOC) (Pena et al 2000). This assessed COPD epidemiology within Spain and reported a prevalence of 9.1% in just over 4000 individuals but interestingly 78% of those labelled with COPD in the study were not previously aware that they had this diagnosis. COPD is no less prevalent closer to home in the UK. In a study of 8215 adults in the UK over the age of 35, 13.3% of the sample had COPD diagnosed by spirometry (Shahab et al 2006). In this study, whilst the relationship between spirometry and symptomatology was not clear, "never smokers" comprised 8.7% of the participants. However, only 18.8% of those diagnosed with COPD by spirometry criteria were actually aware that they had the diagnosis mirroring what was reported in the earlier IBERPOC study. Data suggests that in the UK, COPD accounted for 4.8% of all deaths between 2007 and 2009 whilst annually in the UK, 23,000 people are reported to die from COPD and 24 million working days are lost due to COPD (*Calverley PMA. Chronic Obstructive Pulmonary Disease: the facts. British Lung Foundation; London: 1998*).

1.5 The epidemiology of Chronic Obstructive Pulmonary Disease: Mapping the prevalence of obstructive lung disease in the developing world

Whilst, the burden of COPD in Industrialised developed countries has been well described in the literature, recent estimates suggest that 90% of future COPD deaths will occur in the developing world (McKay et al 2012; *World Health Organization. Chronic obstructive pulmonary disease (COPD) Fact sheet No 315. World Health Organization 2011*). It is therefore of paramount importance to define the prevalence of COPD globally if we are to plan the future health care needs of COPD patients. One such need lies in the prevention of COPD and particularly preventing the complications related to the presence of advanced disease such as decompensated ventilatory failure and Cor Pulmonale. The prevention of patients developing COPD is especially important in low and middle income countries particularly given that access to effective treatments may not be readily available. Integral to this strategy is therefore the identification and avoidance of risk factors associated with the development of airflow obstruction in developing world settings and furthermore describing whether such risk factors differ from those observed in the industrialised developed world where perhaps more is known regarding the epidemiology of COPD. This global burden of respiratory disease is especially felt in countries such as India and China and across much of sub Saharan Africa. Less affluent rural populations living in such countries are particularly vulnerable since they often lack access to adequate healthcare resources (Patil et al 2002). For example, only 27% of India's population of over a billion people live in the urban areas and it is here where 75% of healthcare resources are concentrated (Patil et al 2002).

1.6 The epidemiology of Chronic Obstructive Pulmonary Disease in India

The prevalence of COPD in Indian populations has been described in the main by relatively small scale epidemiological studies. The prevalence of COPD in the literature from India varies from 5% to 12.5 % in males and 3% to 4.2% in females (Jindal et al 2006; Jindal et al 2006). Such variation may be explained by a number of factors such as differences in geographical regions, population studied and methodology used. The rate of smoking reported in the studies varies significantly with a recent review reporting smoking rates of 3.8% to 73.1% in males and 0% to 28% in females and domestic smoke exposure in females showing a similar pattern varying from 38% to 100% reflecting the diverse nature of Indian society (McKay et al 2012). However, a criticism of many of these studies centres on the key limitation of making a diagnosis of COPD purely based on questionnaire criteria in the absence of spirometry (Jindal et al 2001). For example, in one of the largest studies mapping COPD prevalence in India and sponsored by the Indian Council of Medical Research, 35,295 adults greater than 35 years old were surveyed in urban and rural areas of 4 Indian states (Jindal et al 2006). 28.5% of men and 2.1% of women over the age of 15 declared themselves as "ever smokers" and the prevalence of COPD was reported to be 4.1% overall; 5% in men and 3.2% in women. The study reported that 7.7% of smokers were diagnosed with COPD compared with 2.9% of non-smokers supporting the role of tobacco smoke as a key risk factor for COPD as seen in the developed world. However, the form of tobacco consumed also appeared to be relevant. "Bidi" smoking (tobacco packed in a tendu leaf roll), popular in rural Indian regions, appeared to significantly increase the association with COPD when compared with cigarettes. In addition, the authors found that male gender, advancing age and low socioeconomic status were risk factors associated with the finding of COPD but interestingly, not cooking fuel use. However, the authors used the surrogate definition of "chronic bronchitis" rather than using spirometry to define COPD. In one of the earlier

studies where lung function was used in conjunction with symptom prevalence, Joshi et al surveyed 473 employees of in a North Indian mill with a short survey assessing symptoms of "chronic bronchitis" coupled with spirometry. The prevalence of "chronic bronchitis" symptoms was found to be 12.5% overall (20.5% in smokers v 3.9% in non-smokers). The mean FEV1 was found to be significantly lower in those with chronic bronchitis (2.70 litres v 2.97 litres) although the overall prevalence of COPD as diagnosed by spirometry was not clear (Joshi et al 1975).

There is a body of literature describing the impact of well-known risk factors for the development of COPD such as tobacco smoking and biomass fuel exposure (such as when cooking with indoor stoves using animal or plant material as fuel) in India and in other developing countries (Behera et al 1991; Behera et al 1994; Ray et al 1993; Bano et al 2011). The association between biomass fuel exposures with the development of COPD in developing countries is of particular importance in the prevention of COPD given that the population most susceptible to such exposure differs from that seen in industrialised nations i.e. traditionally consisting of "never smoking" females. Such individuals may lack access to appropriate health care resources which have traditionally been concentrated in the cities and more available to upper socioeconomic classes (Patil et al 2002). A recent systematic review and meta analysis of 12 papers concluded that burning wood smoke carried an OR of 4.80 for the development of COPD when the diagnosis was confirmed by spirometry whilst the use of mixed biomass had an OR of 2.49 (Kurmi et al 2010). However, none of these papers in the meta-analysis were from the Indian subcontinent thus highlighting the relative paucity of robust data using spirometry to objectively diagnosis of COPD in the Indian literature.

In industrialised developed countries, the rising incidence of obesity has been linked to the development of respiratory disease (McClean et al 2008; Crummy et al 2008). However, studies conducted in Indian settings have highlighted a relationship between being

underweight, consuming tobacco, and the finding of airflow obstruction. This relationship has not just been observed in India. For example, the authors of the PLATINO study conducted in 5 Latin American cities noted that the risk factors associated with a higher prevalence of COPD included tobacco consumption, advancing age, male gender, lower educational attainment and low Body Mass Index (Menezes et al 2005). However, the PLATINO study categorised BMI into 3 groups: <25 kg/m2, 25-29.9 kg/m2 and ≥30 kg/m2, a grading which may not be representative in a rural Indian population. In a cross sectional study of 99,958 adults in Mumbai over the age of 35 attending a polling station, tobacco consumption was recorded along with Body Mass Index (BMI). Tobacco use, irrespective of whether bidis or cigarettes were consumed carried an OR of 2.46 in men and 3.12 in women for being "underweight" which was defined as BMI <18.5 kg/m2 (Shukla et al 2002). Furthermore, data from urban populations in India have shown reduced FEV1 to correlate positively with being "underweight". A study of 202 COPD patients and 136 controls recruited from a New Delhi Hospital recorded lung function using spirometry, measured BMI and assayed markers of oxidative stress (Vibhuti et al 2007). In the COPD patient group but not the control arm, BMI was found to correlate weakly with percentage predicted FEV1 ($r=0.185$, $p=0.016$). The conclusions from this paper also hint at a possible mechanism behind such an association. Significant correlations were observed between all markers of oxidative stress such as glutathione and percentage predicted FEV1 in the COPD arm but not the control group. Similarly, BMI was found to correlate negatively with an increased oxidative stress status in the COPD patients but not the controls highlighting the importance of the linkage between abnormal lung function and BMI. However, these studies have been conducted in urban Indian settings and it is not known whether the same relationships noted between being underweight and the presence of COPD would be mirrored in rural Indian regions.

1.7 Gaps in the Literature and Opportunities for further research in the field of COPD epidemiology

Whilst the epidemiology of COPD has been extensively studied in the industrialised western world, comparatively little exists in the literature regarding the prevalence of airflow obstruction in rural developing world settings in countries such as India. Thus, there remains a need to both study respiratory symptoms and to define lung function in peoples residing in rural regions of developing world nations such as India if we wish to ultimately improve lung health in these settings. The findings would enable health care professionals working in rural developing world settings to target already limited resources appropriately where they are most needed i.e. for those individuals deemed at greatest risk of either having or developing COPD.

1.8 The Management of Stable COPD

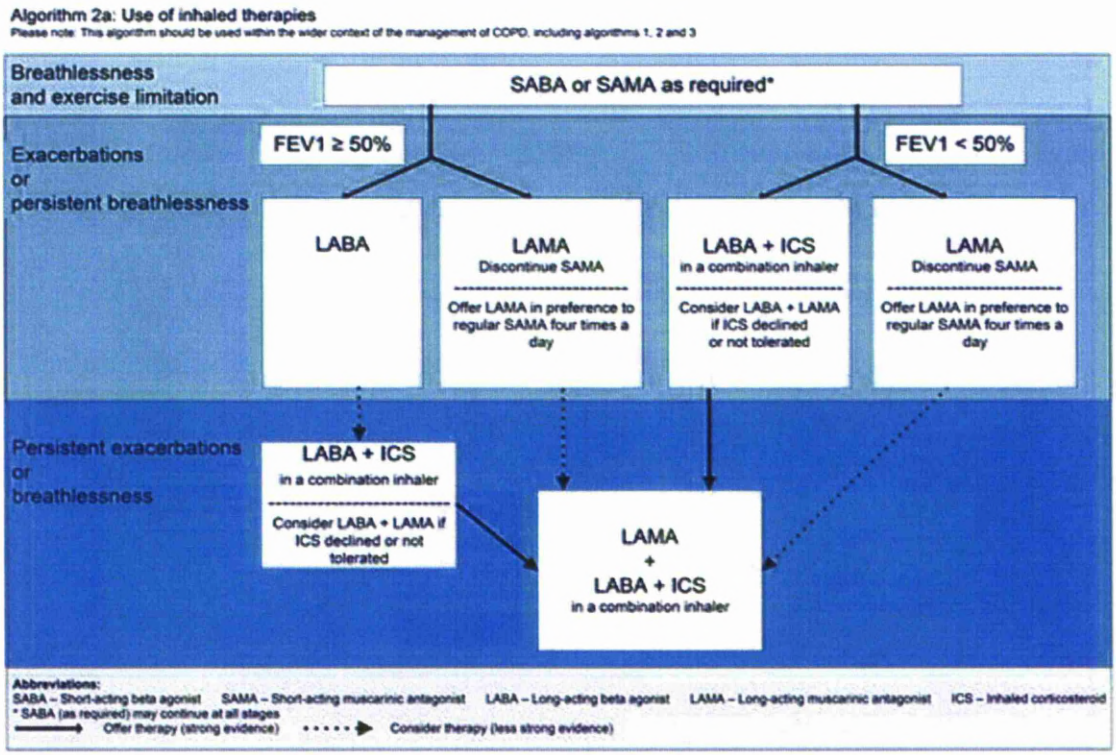
This section deals with both the pharmacological and non-pharmacological aspects of COPD management outside the context of an acute exacerbation (covered in Chapter 2). As COPD is as yet a largely incurable condition, a key strategy in the management of COPD is to identify and diagnose the condition early in the natural history in order to prevent the complications seen as a result of advanced disease. Early identification of COPD could lead to the implementation of smoking cessation measures that may halt the decline in lung function and thus progression of the condition (Kohansal et al 2009). Regarding pharmacological interventions to stop smoking, Nicotine Replacement Therapy, Varenicline or Bupropion is recommended along with attending a support programme *(National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update)*. Data

emerging from a large pharmaceutical trial highlighted a more substantial annual loss of lung function as the severity of COPD increased as defined according to GOLD criteria highlighting the need for early intervention (Tashkin et al 2008). To emphasise this point further, studies conducted both in the UK and abroad have shown that the majority of subjects identified as having COPD were not aware that they had the condition even in the presence of significantly impaired lung function suggesting a need for greater awareness of this condition among healthcare professionals and smokers alike (Shahab et al 2006; Miravitlles et al 2009). All patients regardless of stage should also receive vaccination for influenza and pneumococcus.

Bronchodilator therapy such as short acting beta agonists or short acting anticholinergic drugs are recommended irrespective of the severity of COPD and whether or not one sees an improvement in FEV1 following administration. (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update*). Persistent breathlessness and the presence of exacerbations in those patients with an FEV1 of equal to or greater than 50% of predicted should prompt consideration for maintenance therapy with long acting agents such as muscarinic antagonists and/or beta 2 agonists. In these patients, the prescription of combination therapy in the form of inhaled corticosteroids-long acting beta 2 agonists may be considered in the presence of on-going breathlessness and the development of recurrent exacerbations. An FEV1 less than 50% of predicted with persistent breathlessness in a patient should also prompt consideration of maintenance therapy with long acting agents such as muscarinic antagonists and/or beta 2 agonists but the presence of recurrent exacerbations may also be an indication for the prescription of combination therapy in the form of inhaled corticosteroids-long acting beta 2 agonists (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary*

disease in adults in primary and secondary care. 2010 update; Calverley et al 2007; 356:775-789; Szafranski et al 2003).

Figure 1: Adapted from NICE COPD guidelines 2010



The use of oral theophyllines has been found to be less beneficial and is considered only in selected patients who cannot use inhaled therapies or where these have been unsuccessful. Similarly, the benefits of mucolytic agents are less apparent and again only to be considered in certain subgroups e.g. recurrent exacerbations with chronic cough and sputum production (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update*). Whilst the NICE guidance comments that there is "insufficient evidence" to recommend prophylactic antibiotic therapy in COPD, a recent paper examining the role of

low dose azithromycin therapy reported a significant reduction in the number of exacerbations in the 12 month follow up period (Albert et al 2011).

The prescription of Long Term Oxygen Therapy (LTOT) for a minimum of 15 hours daily has been shown in pivotal trials to reduce mortality and influence disease progression in COPD patients (Calverley et al 1981; NOTT trial 1980). Appropriate patients should have a confirmed diagnosis of COPD, be "clinically stable" and have a PaO2 less than 7.3 kPA on arterial blood gas analysis on two occasions at least 3 weeks apart or have a PaO2 less than 8 kPA in the presence of Cor Pulmonale, secondary polycythaemia or significant nocturnal hypoxaemia (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update*). Ambulatory oxygen is recommended for those patients on LTOT who wish to use oxygen outside the home and in certain patients who are breathless and also exhibit exercise induced desaturation and in whom oxygen aids recovery (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update*). The use of "short burst" oxygen therapy is less certain and has not been shown to reduce the level of breathlessness following a period of exercise in COPD nor aid recovery (Stevenson et al 2004). Interestingly, recent guidance states that short burst oxygen therapy should be considered only in those episodes of severe breathlessness in patients with COPD not relieved by other treatments (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update*).

The role of pulmonary rehabilitation in COPD cannot be over stressed and should be an integral part of COPD management and serves as an adjunct alongside pharmacotherapy and is recommended for those COPD patients disabled by their condition including those who

have been recently hospitalised (*National Institute for Clinical Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. 2010 update; Cochrane Database Syst Rev 2006; 4: CD003793*). Whilst this has been shown to be an effective intervention in terms of reducing breathlessness and reducing health care utilisation, no significant mortality benefit has yet been demonstrated (Griffiths et al 2000).

Finally the place of surgical and other interventional techniques in COPD should not be forgotten. Surgery may include Lung Volume Reduction Surgery which has been shown to carry the greatest benefit to selected subgroups of patients such as those with upper lobe predominant emphysema radiologically and diminished exercise capacity (National Emphysema Treatment Trial Research Group 2003; 348:2059-2073; Edwards et al 2009). Other surgical procedures include bullectomy and in selected cases Lung Transplantation may impart a survival benefit (Lahzami et al 2010). Other interventions which may have a more established role in selected COPD patients include Endobronchial Valve placement bronchoscopically in order to achieve lung volume reduction and reduce hyperinflation (Sciurba et al 2010; 363).

1.9 Predicting survival in COPD: Defining prognostic markers for the clinician

According to GOLD criteria, the severity of COPD is based upon the impairment of FEV1 (Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Revised Version 2011). This classifies a particular COPD patient as having "Mild" to "Very Severe" disease according to the impairment of FEV1 against a given predicted value for that patient. A retrospective study of 78,172 COPD patients reported that the 5 year survival from

the point of being diagnosed with COPD stood at 78% in those classified as having "mild" disease compared to 86% in gender and aged match controls (Soriano et al 2000). However, when taking those patients who were classified as having "severe" disease, the 5 year survival fell to just 30% illustrating a statistically significant elevation in mortality with advancing disease severity according to the reduction in FEV1 ($p<0.01$). Whilst FEV1 offers some prognostic information in COPD for clinicians and epidemiologists, there are limitations when using the FEV1 in isolation in order to understand the impact of COPD in an individual as well as being an absolute prognostic marker. This was illustrated in a review by Jones exploring data from the ISOLDE study which illustrated only a weak correlation ($r=0.23$) between percentage predicted post bronchodilator FEV1 and Health Status as measured by the widely used St George's Respiratory Questionnaire (SGRQ) in 800 COPD patients (Jones et al 2001). Such data highlighted a need for other simple variables which clinicians could easily measure at the clinic or bedside which might predict prognosis in COPD patients. In a Japanese study of 227 COPD patients followed up over 5 years, the degree of breathlessness as measured by the Modified Medical Research Council (MMRC) scale was found to correlate significantly with survival whereas percentage predicted FEV1 did not (Nishimura et al 2002). Returning to the subject of lung function and prognosis in COPD, whilst the use of FEV1 in isolation may carry some drawbacks in terms of a predicting survival, measuring the degree of hyperinflation through static lung function testing may carry greater prognostic value in COPD. This was illustrated by a study of 689 COPD patients followed up over a mean period of 34 months (Casonova et al 2005). 27% had died during the follow up period. The mortality rate was reported as 71% in the subgroup where the Inspiratory Capacity/Total Lung Capacity (IC/TLC) ratio was 25% or less compared with a mortality of 29% where the IC/TLC ratio was greater than 25%, the latter denoting a lesser degree of hyperinflation. The study reported that the IC/TLC ratio had

greater power in predicting survival than the FEV1 alone. The level of exercise capacity has also been shown to predict outcome in COPD as illustrated in a cohort of 156 COPD patients who had completed two 6 minute walk tests approximately 12 months apart. 21% of the group had died after 2 years and the fall in 6 minute walk distance between the 2 tests was significantly higher in this group compared with those that survived. Furthermore, the authors reported that this variable i.e. distance walked in 6 minutes was much more strongly predictive of mortality than percentage predicted FEV1.

In developed world settings, being underweight has been shown to represent an adverse prognostic marker in COPD. In a sample of 2,132 patients with COPD recruited in the Copenhagen City Heart Study, the relative risk (RR) of dying due to COPD was 3.34 in the "underweight" subgroup who were defined as having a BMI less than 20 compared to a RR of 0.72 where the BMI was between 25 and 29.9 (Landbo et al 1999). When taking "all cause" mortality, a lower BMI was associated with an increased risk of death but only in the subgroup of patients classified as having "severe COPD" i.e. FEV1 less than 50% predicted. The recognition of such factors and the limitations of their use in isolation as prognostic indicators in COPD has led to the development of the multi-dimensional "BODE index" (comprising Body Mass index, Degree of Airflow Obstruction, Dyspnoea Index and Exercise capacity) which has been shown to predict the risk of death in combination more accurately than their individual components (Celli et al 2004).

1.10 Definition and burden of COPD exacerbations

An exacerbation of COPD is defined as a "sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset" and may often need a change in the patient's treatment (Rodriguez-Roisin 2000).

COPD exacerbations are the most common cause of medical hospital admission in the UK at a cost of £253 million per year (Wedzicha et al 2007). Recent data suggests that in the UK, up to 12% of acute medical admissions are due to COPD exacerbations and the 3 month mortality following such admissions remains high standing at 15% in a recent report (*The Royal College of Physicians. 2009. Background and rationale for NCROP*). According to the 2008 UK national COPD audit, hospital admissions due to COPD carry a significant in-hospital mortality of 7.7% (*Royal College of Physicians, British Thoracic Society, British Lung Foundation. Clinical Audit of COPD Exacerbations Admitted to Acute NHS Trusts across the UK. 2008*). These data are comparable to earlier studies conducted outside the UK. A 1 year prospective study of COPD patients admitted to a US hospital recorded an overall inpatient mortality of 8% which rose to 16% by 3 months post discharge and stood at 23% by 12 months (Groenewegen et al 2003). Interestingly, in this study, the authors reported that whilst the in-hospital mortality rate was not significantly higher when taking those patients admitted to the Intensive Care Unit with respiratory failure, this rose to 35% when followed up for 1 year. An earlier cross sectional US study analysing the 1996 Nationwide Inpatient Sample (NIS) database analysed 71, 130 patients admitted to hospital with COPD exacerbations (Patil et al 2003). Interestingly the in-hospital mortality was recorded at a lower figure of 2.5% which may be explained by the methodological differences between the studies. Interestingly in this US study, the in hospital mortality for those requiring mechanical ventilation was considerably higher reported at 27.8% but this study was undertaken prior to the widespread use of Non Invasive Ventilatory support. The cause of COPD exacerbations is most often related to infection accounting for the cause of 50% to 78% of cases, either bacterial or viral or due to the combination of both (MacNee et al 2003; Papi et al 2006). So called "infective" exacerbations of COPD have been linked with longer hospital stay, greater impairment of lung function compared to "non-infective" exacerbations (Papi et al 2006).

Other factors implicated in worsening symptoms and causes of exacerbations requiring hospitalization include air pollution, colder outdoor temperature and perhaps more controversially the presence of pulmonary embolism (Peacock et al 2011; Donaldson et al 1999; Tillie-Leblond et al 2006; Rutschmann et al 2007).

The frequency at which exacerbations occurs rises according to increasing disease severity when this is defined by lung function. For example, in a questionnaire based study of 1001 COPD patients conducted in Spain, the authors reported an annual exacerbation rate of 2.3 where the FEV1 was recorded as being less than 40% predicted compared with a figure of 1.6 in the group where the FEV1 was greater than or equal to 60% of predicted (Miravitlles et al 1999). An increase in exacerbation frequency has also been shown to be associated with a more rapid decline in lung function and an increased mortality over 5 years suggesting that within COPD patients, "frequent exacerbators" display a more aggressive disease process (Celli et al 2008;; Donaldson et al 2002; Soler-Cataluna et al 2005).

1.11 Management of COPD exacerbations: Pharmacotherapy

The majority of COPD exacerbations are treated with intensification of bronchodilator therapy whether this is managed at home or in hospital. Antibiotics are often prescribed in COPD exacerbations when patients report an increase in sputum volume and/or purulence along with worsening breathlessness as per the Anthonisen criteria (Anthonisen et al 1987). Oral corticosteroids have been shown to lead to a faster improvement in lung function and recovery time from the exacerbation and also a shorter hospital stay (Davies et al 1999). Criteria on assessment when reviewed in primary care that should prompt admission and management of the exacerbation in hospital rather than at home include severe protracted breathlessness, worsening signs of right heart failure, change in mental state, severe hypoxia

and an inability to cope at home (*NICE clinical guideline 101 – Chronic obstructive pulmonary disease 2010*). In patients admitted to hospital, the role of intravenous aminophylline in acute exacerbations has been reported to be less beneficial in terms of improving outcomes. Duffy et al studied 80 COPD patients presenting with an acute exacerbation randomising 39 to intravenous aminophylline and 41 to placebo (Duffy et al 2005). Over a 5 day period, there was no difference between change in FEV1 and FVC between the 2 arms and overall, no difference in mortality or length of hospital stay. Interestingly, after 2 hours, the aminophylline group showed a significantly greater fall in PaCO2 and rise in arterial pH compared to the placebo group.

1.12 Oxygen therapy during acute exacerbations of COPD and the phenomenon of Oxygen induced hypercapnia

The British Thoracic Society recommends oxygen to be prescribed to achieve a target saturation of 88-92% in those at risk of hypercapnia (BTS Guideline for Emergency Oxygen Use in Adult Patients 2008). The adverse effects of oxygen-induced hypercapnia in COPD have been well established for decades (Campbell et al 1960). The classical teaching to explain oxygen induced hypercapnia in COPD relates to uncontrolled "high flow" oxygen eliminating the hypoxic drive to breathe which is governed by chemoreceptors situated in the aortic arch and carotid body (Dunn et al 1991). In reality, the mechanisms behind oxygen induced hypercapnia are multifactorial comprising suppression of hypoxic drive as well as ventilation-perfusion mismatching and to a small extent, the Haldane effect. Ventilation-perfusion mismatch in this setting refers to the lifting of hypoxic vasoconstriction where the presence of hypoxia due to the damage sustained by these lung units resulted in a diversion of blood flow from these poorly ventilated units. Uncontrolled "high flow" oxygen therapy in

this situation would reverse this diversion of blood flow but the damaged lung units now perfused and receiving this blood flow remain ineffective as gas exchanging structures thus resulting in further accumulation of CO2 in the blood. Practically this is observed by an increase in Dead Space Ventilation. Aubier et al studied 22 COPD patients in the acute setting who had been given "100% oxygen" (Aubier et al 1980). Whist Minute Ventilation fell by 18% early on during the study period, by the end of the period, it had risen to 93% of the control value. The PaCO2 in the group rose significantly by 3.06kPA by the end of the period but was not found to be correlated to any decrease in Minute Ventilation but was linked mainly to an increase in Dead Space Ventilation secondary to Ventilation-perfusion mismatch. Sassoon et al also reported that it was in fact the alteration in Ventilation-perfusion relationship manifested by dead space to tidal volume ratio (VD/VT) rather than changes in Minute Ventilation or Respiratory Drive that was most closely linked to the increase in PaCO2 when studied in 17 COPD patients in the stable state (Sassoon et al 1987). Robinson et al studied 22 patients admitted to hospital with an acute exacerbation of COPD within 72 hours of admission (Robinson et al 2000). Each subject breathed 100% oxygen for 20 minutes with "pre and post" arterial blood gas values and Ventilation-Perfusion distribution studies performed. 12 patients were classified as CO2 "Retainers" where the mean CO2 increased by 1.17kPA and here the Minute Ventilation fell by 20% following the period of breathing 100% oxygen. In contrast, the Minute Ventilation did not change significantly in the "Non Retainers" group whereas the degree of VQ mismatching was no different between the "Retainers" and "Non Retainers." Therefore, the results of this study support the view that it is in fact a reduction in Ventilation due to removal of hypoxic drive rather than changes related to ventilation-perfusion maldistribution which determine the further rise in CO2 as a result of hyperoxia.

Moving away from the laboratory, a study of 405 patients emphasised the "real life" consequences of uncontrolled oxygen therapy during acute exacerbations of COPD (Austin et al 2010). 214 of these subjects had a diagnosis of COPD conducted in a pre-hospital setting illustrated a significantly higher mortality in an "un-titrated high flow" oxygen group compared to a group where oxygen was "titrated" to 88-92% oxygen saturation in those with a history of COPD. The authors reported that in those patients with a confirmed diagnosis of COPD, titration of oxygen saturation between 88-92% reduced the risk of death by 78%. The dangers were further illustrated in a study of 983 patients admitted with an acute exacerbation of COPD over a 12 month period to a large city hospital in England (Plant et al 2000). 199 presented with a respiratory acidosis (defined as arterial pH <7.35 with PaCO2 >6kPA) and of these 199 "acidotic patients", the pH normalised from transfer from Accident and Emergency to the ward in 20%. The respiratory acidosis normalised in 32% of patients with an initial PaO2 greater than 13.3 kPA compared with 13% of patients with an initial PaO2 < 7.3 kPA without the need for Ventilatory support. The only difference between the "pH normalisers" and "non-normalisers" was in the initial PaO2 checked on the blood gases (median PaO2 10.3 kPa v 8.49 kPa; p=0.01) hence normalisation of pH was linked to reducing the concentration of inspired oxygen. The findings from such papers have prompted national guidance from the British Thoracic Society to recommend that oxygen should be prescribed to achieve a target saturation of 88-92% in those at risk of hypercapnia such as those with COPD who have either been known to have presented with type 2 Respiratory failure or deemed at risk of doing so (BTS Guideline for Emergency Oxygen Use in Adult Patients 2008).

Despite the above management, about 20% of COPD exacerbations present with decompensated ventilatory (i.e. Type 2 respiratory) failure on admission characterised by an arterial pH below 7.35 and PaCO2 greater than 6.0kPa which may not be reversed with the

"medical management" described above (Plant et al 2000). In this scenario, simply administering oxygen therapy will not improve the patient's clinical condition and this situation represents an indication to consider Ventilatory Support.

1.13 The pathophysiology of COPD exacerbations: Relationship with abnormal gas exchange and acute ventilatory failure

In contrast to that seen in healthy individuals, patients with severe COPD have been shown to exhibit a positive pressure in the alveolus at the end of expiration which makes the generation of a negative pressure, a pre-requisite in order to draw fresh air into the lungs, more difficult (Haluszka 1990). The magnitude of this positive pressure is called intrinsic PEEP or auto PEEP (PEEPi) and is measured conventionally with the insertion of an oesophageal balloon (Petrof et al 1990). In a study of 96 COPD patients studied in the stable state, PEEPi was found to be present in 67% ranging from 7-9cmH20 (Haluszka 1990). The clinical consequence of PEEPi means that in order to draw fresh air in their lungs to partake in gas exchange, COPD patients have to overcome the magnitude of the PEEPi to get to the starting point of healthy individuals i.e. "Zero pressure." Up to 40% of the Work Of Breathing (WOB) may be spent overcoming PEEPi before a negative pressure is reached (Appendini et al 1999; Smith et al 1988; Ranieri et al 1993).

A number of studies have attempted to understand the pathophysiology underlying acute exacerbations of COPD in comparison to that seen in the stable state as well as mapping these changes during the recovery from the exacerbation. Stevenson et al recruited 22 patients presenting with COPD exacerbations within 24 hours of hospital admission and followed them until discharge and beyond (Stevenson et al 2005). The Inspiratory capacity (IC) was measured at 62% of predicted rising to 73% of predicted at the time of discharge from

hospital and increasing further to 81% of predicted by Day 42. Interestingly, the rise in FEV1 over this period in the study population was less impressive starting at 47% on admission, 51.2% by discharge from hospital and 54.8% by day 42. The data suggest that it is the phenomenon of dynamic hyperinflation as denoted by the changes in IC which appear to be the most striking abnormality during an exacerbation and is associated with increasing breathlessness rather than the static lung volumes as measured by the FEV1. Similar findings were also reported by Parker et al studying 20 acute exacerbations of COPD admitted to a Canadian hospital who were followed up for a 60 day period (Parker at al 2005). Here, the improvement in breathlessness as patients recovered from the exacerbation appeared to correlated most significantly with an improvement in Inspiratory Capacity and Vital Capacity denoting a lesser degree of dynamic hyperinflation. Whilst none of the subjects in these 2 papers had decompensated ventilatory failure, it is conceivable that the mechanisms described above would be even more relevant in such a scenario. Studies have shown that in setting of acute decompensated ventilatory failure complicating COPD, the magnitude of PEEPi is even higher than that seen when studied in the stable state and the absolute level is greater than in other disease states where abnormal gas exchange may also occur. For example a study of COPD patients during acute exacerbations reported a PEEPi of 13-22 cmH20 compared to 3cmH20 in a group with pulmonary oedema (Broseghini et al 1988; Fleury et al 1985). The presence of a significant degree of PEEPi, to the level observed in these studies, may mean that the patient's inspiratory efforts on their own may not be sufficient to trigger the ventilator thus causing worsening gas exchange and ineffective ventilation. In the acute setting, the situation is further worsened by a more pronounced degree of rapid shallow breathing promoting further hyperinflation (not enough time to breathe out hence more air trapping occurs).

Studies have shown that a significant proportion of patients admitted to hospital with COPD presents in a state of decompensation characterised by respiratory acidosis and acute Hypercapnic Respiratory Failure (AHRF); pH <7.35 & PaCO2 >6.0 kPA). In a study of 983 patients presenting to a large UK city teaching hospital, 20% were found to have a respiratory acidosis on admission (Plant et al 2000) whilst in the latest UK audit of COPD exacerbations admitted to hospital comprising 9716 patients from 232 units, a similar proportion of patients, 20%, exhibited a respiratory acidosis on admission (Roberts et al 2011). Respiratory acidosis and acute hypercapnic respiratory failure often arise because there is an imbalance between the load imposed on the respiratory system and the inability of the patient's respiratory system to cope with that load e.g. due to inadequate respiratory drive e.g. due to sedatives or in some disease states, reduced respiratory muscle strength. Thus, the respiratory system fails to function effectively as a pump resulting in an inability to eliminate carbon dioxide which accumulates in the blood. This worsening hypercapnia results in lowering of the arterial pH and the development of acute respiratory acidosis. Respiratory acidosis "begets" itself further compromising the respiratory muscles and ultimately resulting in death if left untreated (Elliot et al 2005; Jeffrey et al 1992). The presence of respiratory acidosis complicating acute exacerbations of COPD represents a medical emergency and is an indication for assisted ventilation (Chakrabarti et al 2005).

1.14 The administration of Positive Pressure Ventilation in the management of acute decompensated ventilatory failure complicating COPD exacerbations: Physiological rationale and mechanisms of action

The first description of Artificial Ventilation dates back to 1530 when Parcelus (AD 1493-1541) used the "fire bellows" to ventilate a patient via a tube placed in a patient's mouth

(*Pilbeam, SP. Mechanical Ventilation 2nd Ed. ©1992 Mosby-Year Book, Inc*). Whilst the majority of practising clinicians today view the term "Mechanical Ventilation" as synonymous with "Positive pressure Ventilation", it was in fact Negative Pressure Ventilation which first gained foothold as the treatment of choice for respiratory failure in the acute setting. The principle of negative pressure ventilation differs in that it relies on creating a sub-atmospheric pressure around the chest wall by means of enclosing the chest and abdomen in a rigid chamber resulting in air being drawn into the lungs. However, the process of breathing out in such a system is a passive one dependent on the elastic recoil of the respiratory system i.e. the chest wall and lungs deflating back to their resting state (Shneerson 1991) The first "negative pressure" ventilator for mainstream clinical use was developed by Drinker in 1928 and negative pressure ventilation in the form of the so called "iron lung", "cuirass" or "tank ventilator" depending on the form of encasement chamber used represented the mainstay of life support during the polio epidemics in the 1930s to the 1950s (Drinker and Shore 1929). Indeed, it was during the latter part of these polio epidemics that positive pressure gained prominence as due to a shortfall of ventilators and an excess of acute respiratory failure cases, medical students resorted to hand pumping positive pressure into the lungs of patients 24 hours a day thus keeping them alive (Lassen 1953). This coupled with the fact that negative pressure ventilators were cumbersome and more limited in function led to them being superseded by more compact and effective positive pressure ventilators from the 1960s onwards.

Traditional concepts dictate that in the acute setting, ventilatory support is administered in the Intensive Care Unit (ITU) using an endotracheal tube; so-called" Invasive Positive Pressure ventilation (IPPV)". However IPPV carries a significant burden in terms of morbidity, complications, mortality, cost and Length of Stay (LOS) (Girou et al 2000). At first glance, given the already significant levels of air trapping and auto-PEEP already present in a COPD

patient admitted to hospital with an acute exacerbation complicated by respiratory acidosis, it may seem counterintuitive to deliver further positive pressure to the airway in an attempt to improve gas exchange as this may worsen hyperinflation further. However, the application of external PEEP to the airway in an attempt to offset intrinsic PEEP is described elegantly in the so called "waterfall theory" by Dr Martin Tobin (Tobin *PEEP, auto-PEEP and waterfalls* 1989).

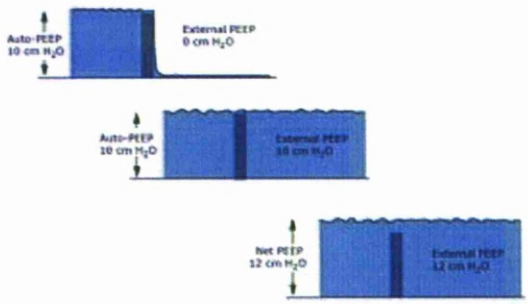


Figure 2: Adapted from Tobin et al Chest 1989; 96: 449-51

The rationale of this is lies in that as long as the level of water downstream to the waterfall in the valley below (i.e. representing the externally applied PEEP given by the Ventilator) does not rise above the level where the water flows off the cliff into the valley, there will not be any disruption to the how the waterfall works (see figure 1). However, increasing the level of externally PEEP above this threshold point (known as pcrit representing about 85-86% of the level of PEEPi) has been shown to increase End Expiratory Lung Volume this worsening dynamic hyperinflation and gas exchange (Georgopoulos et al 1993; 4: 197-203; Nava et al 1993). The concepts listed above have been applied specifically to the setting of Non Invasive Ventilaion in AHRF complicating COPD. Appendini et al recruited 7 COPD patients with AHRF and studied respiratory mechanics in 4 phases: a) Spontaneous Breathing

b) Continous Positive Airways Pressure (CPAP) c) Inspiratory Positive Airways Pressure (IPAP) alone d) IPAP & PEEP with d) representing how NIV is current delivered i.e. IPAP and EPAP (Appendini et al 1994). PEEP was measured using oesophageal balloon in all cases through which the WOB measured by using the transdiaphragm time product (PTPdi). PEEP was set at 80-90% of PEEPi according to the rationale of the "Waterfall theory" and also based on the previous data showing that the ideal PEEP represented a threshold value of 85-86% of PEEPi (Georgopoulos et al 1993; Nava et al 1993).The study by Appendini et al showed the greatest decrease in WOB (i.e. PTPdi), improvement in gas exchange and greatest increase in Minute Ventilation was seen with the NIV mode i.e. IPAP & PEEP (Appendini et al 1994).

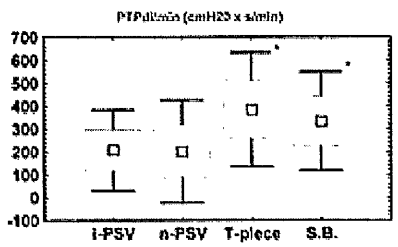
This work has subsequently led to the recognition that the delivery of "optimal" PEEP in acute COPD exacerbations follows a "U shaped curve" (i.e. too little external PEEP will be ineffective whilst too much may paradoxically worsen hyperinflation) with attempts to define the concept of what represents the "best PEEP" in COPD patients undergoing mechanical ventilation (Ranieri et al 1993; Guerin et al 2000) i.e. physiologically tailoring ventilation to the individual patient by abolishing PEEPi.

1.15 Non Invasive Ventilation in the management of respiratory acidosis and decompensated ventilatory failure complicating COPD exacerbations: Indications and reviewing the evidence to date

Non-invasive ventilation (NIV) refers to the administration of Ventilatory support in a manner foregoing the need for an endotracheal tube, sedation and paralysis. In the acute scenario, NIV implies that positive pressure is delivered to the patient's respiratory system usually by means of an interface such as a tightfitting face or nasal mask. From a

physiological perspective, NIV administered in the correct manner and in an appopriate clinical context has been shown to be an effective substitute for IPPV. Appendini et al studied 12 COPD patients presenting with acute hypercapnic respiratory failure in 4 different modes: a) T piece trial b) IPPV (termed "i-PSV") c) Spontaneous breathing (S.B) d) NIV (termed "n-PSV) (Appendini et al 2001). The work of breathing, degree of diaphragmatic loading and energy consumed by the diaphragm as measured by the diaphragmatic pressure-time product (PTPdi) was lowest with the NIV and IPPV modes and was not shown to differ significantly between the Non Invasive and Invasive modes (see figure 2). Furthermore, the expired tidal volume was significantly higher with the NIV and IPPV and again did not appear to differ between the 2 modes of Ventilation and interestingly, the level of intrinsic PEEP was lowest in the NIV arm.

Figure 3: Adapted from Appendini et al 2001



Whilst comparatively few studies exist which speculate on the mechanisms behind the effectiveness of NIV in the acute setting, data from studies conducted when NIV is administered to COPD patients in the stable state suggest that the improvement in blood gases occur through a decrease in lung hyperinflation and through NIV altering the ventilatory sensitivity of the respiratory system to carbon dioxide (Nickol et al 2005; Nickol et al 2008; Diaz et al 2002).

NIV has not only been shown to be an effective treatment for respiratory acidosis complicating a COPD exacerbation but has now become the gold standard of care in this scenario following the result of randomised controlled trials illustrating a reduction in intubation rate, improved mortality and quicker relief of breathlessness (Bott et al 1993, Plant et al 2000, Brochard et al 1996; Kramer et al 1995; Angus et al 1996). It is conceivable that the improved outcomes observed during acute COPD exacerbations when ventilation is administered non-invasively is linked to a reduction in Ventilator acquired pneumonia and other nosocomial infections related to ITU admission as well as foregoing the need for an endotracheal tube or tracheostomy which bypasses the upper airway (Girou et al 2000; Girou et al 2003). Furthermore, when ventilation is given in a Non Invasive fashion, consciousness is preserved along with maintenance of airway defences and allows the patient to eat, drink and communicate. In a case control study conducted in a French ITU, 50 patients treated with NIV for acute COPD exacerbations or cardiogenic pulmonary oedema were compared with 50 patients where IPPV was administered (Girou et al 2000). Both groups were matched for severity of physiological derangement at presentation and diagnosis. The overall rate of nosocomial infections was significantly higher in the IPPV group (38% v 14%; p=0.006) as well as nosocomial pneumonia (22 v 8%; p=0.04). The crude ITU mortality was significantly higher in the IPPV group (26 v 4%; p=0.002). The risks of invasive ventilation was further highlighted by a multinational survey of 42 ITUs followed the clinical course of 689 patients presenting with acute respiratory failure (Carlucci et al 2001). 15% of the group had hypercapnia i.e. AHRF whilst 48% had hypoxaemic respiratory failure. 108 were treated with NIV whilst 380 received IPPV following endotracheal intubation. The number of patients with AHRF was approximately equally divided between NIV and IPPV; no patient with coma received NIV and comparatively few patients with acute hypoxaemia received NIV. The incidence of nosocomial pneumonia was significantly less in the NIV group (10 v 19%;

$p<0.05$) and the mortality rate was also significantly lower in the NIV group (22% versus 41%; $p < 0.001$)

In one of the early randomised controlled trials involving NIV during acute exacerbations of COPD, Bott et al assigned 60 COPD patients presenting with AHRF (defined as $PaO2 < 7.5$ kPa, and $PaCO2 > 6$ kPa) to either "standard" therapy or "NIV+standard therapy" (Bott et al 1993). Of the 30 patients randomised to the NIV arm of the study, 4 did not actually receive NIV for various reasons e.g. confusion, unable to tolerate nasal interface. When the entire group was analysed including the whole 30 patients randomised to NIV (intention to treat), there was no significant difference in mortality (3/30 NIV arm v 9/30 standard therapy arm; $p=0.106$). However, when one excluded these 4 patients who did not actually get NIV despite being randomised to the NIV arm, the administration of NIV appeared to significantly improve mortality (1/26 v 9/30; $p=0.014$). However, the mean overall pH of those patients entering the trial was 7.35 perhaps not entirely representative of those receiving acute NIV in daily clinical practice. Despite the limitations in analysis, the message emerging from the paper at the time was that NIV could have a major role in AHRF due to acute COPD exacerbations.

In another randomised controlled trial involving NIV, of 85 COPD patients admitted to a French ITU with respiratory acidosis, 42 were assigned to "standard therapy' arm ($n=42$; mean pH 7.28) whilst 43 were assigned to a "Non-Invasive Ventilation" arm ($n=43$; mean pH 7.27). 31 (74%) of the "standard therapy" group required endotracheal intubation and IPPV within the first 12 hours of the hospital stay compared to just 11 subjects (26%) in the NIV arm ($p<0.001$) (Brochard et al 1995). The overall complication rate in the "standard therapy" group was shown to be significantly higher than in the "Non Invasive Ventilation" group (48% v 16%; $p=0.001$). For example, seven patients (17%) in the "standard therapy" group succumbed to pneumonia and 2 of these patients died as a result of pneumonia. This

compared to only 2 (5%) patients in the "non-invasive ventilation" arm developing pneumonia with no fatalities reported here. Furthermore, the in-hospital mortality and the "length of hospital stay" of the "standard treatment" group were significantly higher compared with the NIV arm (29 v 9% in hospital mortality; 35 v 23 days length of hospital stay). This ITU based study not only highlighted the potential complications and adverse outcomes resulting from endotracheal intubation and IPPV but also the benefits of Ventilatory support when administered in a non-invasive manner.

A landmark prospective randomised controlled multicentre trial conducted in the UK not only demonstrated the benefits of NIV over "standard" therapy in acute COPD exacerbations but also demonstrated the feasibility and effectiveness of NIV when administered in a ward based setting (Plant et al 2000). In a study of 236 acute COPD exacerbations complicated by respiratory acidosis i.e. with a pH 7.25-35 and PaCO2>6kPA, 118 were randomised to "standard" therapy whilst 118 were assigned to "NIV". The NIV arm witnessed a 44% reduction in intubation rate (18 (15%) required intubation in NIV group; 32 in standard arm (27%) as well as a 50% reduction in mortality (12 died in NIV group; 24 died in standard arm). Furthermore, NIV use led to a more rapid relief of breathlessness compared to that seen in the "standard" arm. Interestingly, in this study, the mean pH of patients entering the trial was 7.32 representing a relatively mild degree of respiratory acidosis. The 2008 UK COPD audit showed that of all patients receiving NIV for AHRF, 55% had an arterial pH less than 7.26 indicating a more severe degree of respiratory acidosis than that seen in some randomised clinical trials (Roberts et al Thorax 2011; Plant et al 2000; Bott et al 1993). Bearing this in mind, NIV has also been shown to benefit patients with more severe degrees of respiratory acidosis both in the context of randomised controlled trials and observational studies, (Conti et al 2002; Carlucci et al 2002). For example, In an Italian ITU based study, 49 patients with a mean baseline pH of 7.20 were randomised to receive NIV (n=23) or

endotracheal intubation and IPPV (n=26). 48% of patients in the NIV arm avoided IPPV. Interestingly, the administration of NIV appeared to convey some long term benefit. At 12 months, the NIV arm showed a reduced rate of hospital readmission (65 v 100%) and less likelihood of being prescribed Long Term Oxygen Therapy (LTOT) (0 v 36%). (Conti et al 2002). However, it must be stressed that the study by Conti et al, where the degree of acidosis at baseline was more severe, was performed in the ITU setting in comparison to the study by Plant et al which was conducted in a general ward where the mean pH at entry was 7.32 indicating a less severe respiratory acidosis.

Comparatively little exists in the literature regarding comparisons between NIV and the respiratory stimulant Doxapram during acute exacerbations of COPD. In a randomised controlled trial, Angus et al compared 9 patients who were administered NIV with 8 patients given Doxapram (Angus et al 1996). The mean pH was 7.30 in the Doxapram arm compared with 7.31 in the NIV arm. There was no significant improvement in PaCO2 in the Doxapram arm (starting at 10.1 kPA) whilst the PaO2 improved transiently but was not maintained by 4 hours into Doxapram treatment. In contrast, the PaCO2 fell from 10.1kPA to 8.7kPA ($p<0.05$) and there was a statistically significant improvement in PaO2 with NIV (5.9 to 8.1kPA; $p<0.05$). 3 patients died in the Doxapram group leading to an alteration in the study protocol allowing the addition of Ventilatory support in this group whilst the entire NIV arm survived to discharge.

Therefore, given the evidence base, NIV should be considered in patients presenting with acute exacerbations of COPD where a respiratory acidosis (pH < 7.35; PaCO2>6.0kPA) persists despite maximal medical treatment on controlled oxygen therapy (British Thoracic Society Guideline; Non Invasive Ventilation in Acute Respiratory Failure; 2002). Absolute contraindications to the administration of NIV include the presence of facial trauma or burns, recent upper airway facial surgery, active vomiting and obstruction to the upper airway. NIV

should be administered early on during the course of a respiratory acidosis complicating acute exacerbations of COPD in order to gain the maximal benefits ensuring also that the patient has received controlled oxygen therapy and optimal medical management e.g. bronchodilator therapy, corticosteroids and antibiotics.

1.16 Predictors of outcome in acute hypercapnic respiratory failure treated with Non Invasive Ventilation in the context of COPD exacerbations

Despite the body of literature clearly demonstrating the benefits of NIV for AHRF complicating COPD exacerbations, in some cases, NIV administration fails to improve respiratory acidosis necessitating endotracheal intubation and IPPV, or in the case of those patients where IPPV is considered an inappropriate intervention, palliation. Varying rates of NIV failure have been reported in the literature in the context of COPD in the acute setting ranging from 5-52% (Bott et al and Kramer et al: 9% failure rate; Conti et al 52% failure rate) depending on the study design and case mix i.e. randomised controlled trial or analysis of large unselected cohorts. Regarding the latter, a group from Italy reported their experience of NIV over time from 1992 to 1999 (Carlucci et al 2003). The rate of NIV failure over the whole period was 17%. A failure rate of 18% was observed between 1992 and 1996 (145 cases in total) and this fell to 16% between 1997 and 1999 (63 cases). Interestingly, the arterial pH at baseline in NIV "successes" and "failures" during the 1992-1996 period was 7.26 and 7.21 respectively. However, between 1997 and 1999, the baseline arterial pH fell in both groups to 7.21 and 7.18 in "successes" and "failures" implying that "sicker" patients i.e. those with a more severe degree of respiratory acidosis were being ventilated successfully in the latter period as experience with NIV grew (Carlucci et al 2003).Another Italian study of unselected COPD exacerbations charted the failure rate of NIV in 1033 patients admitted

with respiratory acidosis into 13 centres comprising a mixture of ITUs, General Wards and Respiratory Intermediate Care Units and reported that NIV failed in 236 (22.9%) (Confalonieri et al 2005). In the 2008 UK COPD audit, the inpatient mortality of 1077 patients receiving NIV was 25% and only 34 (3.2%) of the 1077 NIV patients went on to receive IPPV (Roberts et al 2011).

A number of variables have been reported to be associated with an increased risk of NIV failure when patients are admitted with AHRF complicating acute exacerbations of COPD. These are listed in table 1 and discussed in detail the section below.

Table 2

- Arterial blood pH and Respiratory Rate at baseline and trend following initiation of NIV
- Pneumonia and excessive secretions
- Illness Severity Scores e.g. APACHE 2/SAPS 2
- Impaired consciousness
- Metabolic dysfunction
- Body weight
- Excessive leak and tolerance of NIV
- Lung Function
- Bacterial colonisation of the lower airway e.g. Gram negative organisms
- Humidification of pressurised gas

a) **Arterial blood pH and Respiratory Rate at baseline and trend following initiation of NIV:** The baseline severity of acidosis, hypercapnia and tachynoea (Respiratory Rate) along with the change in such variables in the first few hours after

NIV has been commenced has been linked to final outcome. One of the earlier randomised control trials of NIV in acute COPD exacerbations conducted by Bott et al found that the patients who died following NIV initiation were more acidotic (mean pH 7.310 v 7.347) and hypercapnic (9.4 kPA v 8.4 kPA) when compared with those who survived. However, it is noteworthy that in this study, the mean pH of the entire "NIV" arm was 7.348 showing only a mild degree of respiratory acidosis (Bott et al 1993). The ward based randomised control trial by Plant et al reported that a failure of the Respiratory Rate (RR) and PaCO2 to fall along with a failure of the arterial blood pH to rise from 1 to 4 hours following the initiation of NIV was linked to a poor outcome i.e. need for intubation and IPPV (Plant et al 2000). Furthermore in this study, when taking the subgroup of patients with a pH<7.30 i.e. those with more severe respiratory acidosis, there were no significant differences between mortality (22 v 34%; p=0.31) and for meeting criteria for endotracheal intubation (36% v 42%) between the NIV and standard arm respectively although the study itself was specifically powered for subgroup analysis. However, the practical message inferred from this data was that clinicians should be cautious about administering NIV in a ward based environment in patients exhibiting more severe levels of respiratory acidosis where certain trials have shown an increased likelihood of NIV failure. In such circumstances, one may opt for admission to a HDU environment if such patients are a candidate for escalation to endotracheal intubation and IPPV. A large observational study of 1033 in a variety of settings (ITU, Special Respiratory Care Unit, Medical Ward) found that a baseline pH <7.25 carried an OR of 1.97 for NIV failure ($p<0.05$) and this increased dramatically to 21.02 if the pH failed to climb above 7.25 more than 2 hours following NIV initiation ($p<0.0001$) thus highlighting the prognostic impact of more severe degrees of acidosis. The authors observed a

similar relationship when taking the baseline and 2 hour Respiratory Rate (baseline RR of 30–34 min (OR=1.83, p<0.05); baseline RR>35 breaths·min−1 (OR=2.66, p<0.001); 2 hour RR of 30–34 min (OR=2.67, p<0.001) or 2 hour RR>35 min (OR=4.95, p<0.001)) (Confalonieri et al 2005).

A retrospective analysis of 59 episodes of AHRF complicating COPD exacerbations (78% success rate; 8.5% mortality) also suggested that baseline pH was significantly lower in the "NIV failures" (mean 7.22) compared to the "NIV successes" (mean 7.28) (Ambrosino et al 1995). Soo Hoo et al observed 14 episodes of decompensated AHRF in 12 COPD patients treated with NIV in an American ITU based study with a 50% success rate. Interestingly, unlike the previous reports, the baseline arterial pH was not significantly different between the "NIV successes" and "failures" (pH 7.26 in both arms) (Soo Hoo et al 1994). Other authors have also failed to find an association between baseline pH prior to commencing NIV and final outcome. Anton et al reported that it was rather the finding of an improvement in arterial pH after 1 hour of commencing NIV which was linked to a favourable outcome. Here, in a prospective study of 44 episodes of AHRF in 34 COPD patients, the mean pH in both NIV "successes" (n=34) and "failures" (n=10) were not significantly different at baseline (7.27 v 7.28 respectively) but differed by 1 hour following commencing NIV (7.34 v 7.28; p<0.05) (Anton et al 2000).

b) **Pneumonia, secretions and outcome from NIV:** The issue of whether community acquired pneumonia (CAP) represents a risk factor for failure of NIV is controversial. A retrospective analysis by Ambrosino et al found that a clinical diagnosis of pneumonia was found in 38.5% of "NIV failures" compared with 8.7% of "NIV successes" (Ambrosino et al 1995). These findings appeared to be backed up by a prospective observational ITU based study published in 2001 where NIV was

administered to 24 patients with AHRF complicating a diagnosis of pneumonia but in the *absence* of COPD. In this study, 66% eventually required endotracheal intubation and IPPV (Jolliet et al 2001). In the observational study by Soo Hoo et al, pneumonia with excess secretions was found to be present in 3 of the 7 "unsuccessful" NIV episodes and this was cited by the authors as a risk factor for an unfavourable outcome (Soo Hoo et al 1994). However, Confalonieri et al randomised 56 patients with pneumonia to NIV or "standard therapy" in ITU. 23 patients of the 56 had a diagnosis of COPD and all were hypercapnic. 12 patients had COPD in NIV arm and 11 were in the "standard therapy" group. COPD patients with CAP randomised to NIV were significantly less likely to require intubation (0% v 55%) and showed a statistically significant improvement in 2 month mortality (89% v 36%) and a decreased ICU stay (0.25 days v 8 days) (Confalonieri et al 1999). Such data suggests that the presence of pneumonia on the background of an established diagnosis of COPD may herald a more favourable outcome from NIV in AHRF compared to those cases where there is no underlying chronic lung disease. In the latter situation, the presence of hypercapnia may all be resulting from acute pneumonic sepsis resulting in a rapid and significant level of oxygen desaturation particularly when the mask is removed and an increased likelihood of treatment failure and cardiorespiratory arrest. Such patients should be managed in a HDU/ITU setting where they may be closely observed and facilities for intubation and IPPV are readily available. The issue of "secretions" independent of pneumonia has also been shown to increase risk of NIV failure. In a prospective survey by Carlucci et al, the presence of "copious secretions" were noted in 34% of the "NIV failures" compared with just 14% of the "NIV successes" ($p<0.05$) hence making this a relative caution for clinicians when considering a patient for NIV in the acute setting (Carlucci et al 2001).

c) **Illness Severity Scores and outcome from NIV:** Scoring systems such as the APACHE 2 score or SAPS II scale are commonly used in the ITU setting to measure severity of illness (Knaus et al 1985 ; LeGall et al 1993). The utility of such scoring systems in predicting the outcome of NIV particularly in the context of AHRF complicating COPD has yielded conflicting results in the literature. In the small observational patient study by Soo Hoo et al, the mean APACHE 2 score in the 7 NIV "successes" was 15 compared to 21 in the 5 NIV "failures" ($p=0.02$) (Soo Hoo et al 1994). In a retrospective review of 59 episodes of AHRF in COPD treated with NIV, Ambrosino et al also found a significant difference between NIV "successes" and "failures" (18 v 24; $p<0.0001$) (Ambrosino et al 1995). Confalonieri et al prospectively charted the outcome of 1033 COPD patients treated with NIV in the acute setting and found that an APACHE II score ≥ 29 at baseline carried an OR of 3.30 for NIV failure and this increased to 4.79 if this score persisted 2 hours following NIV initiation ($p<0.001$) (Confalonieri et al 2005). Similarly Carlucci et al found the APACHE 2 score to be significantly lower in the NIV "successes" v "failures" in both the 1992-96 (21 v 25; $p=0.005$) and the 1997-99 cohorts (24 v 29; $p=0.006$) (Carlucci et al 2002). However, in this study, just as was seen with arterial pH as a prognostic marker, the APACHE 2 scores in the NIV "successes" during the latter 1997-99 period were similar to the NIV "failures" charted during the early 1992-1996 cohort implying that the group were gaining experience in successfully ventilating "sicker" patients using NIV (Carlucci et al 2002). In a subgroup of "sicker" patients with a lower baseline mean arterial pH (mean of 7.20), 52% of patients failed to improve with NIV and this subgroup has a mean SAPS II score which was significantly higher than the subgroup where NIV was successful (39 v 35) (Conti et al). However, other authors have not found scoring systems such as the

APACHE 2 to be a prognostic marker in such a setting (Anton et al 2000, Meduri et al 1996).

d) **Impaired consciousness and outcome from NIV:** During the early experience with NIV in AHRF, the presence of impaired consciousness or encephalopathy (implying an inability to adequately protect the airway) was felt to represent a relative contraindication to the use of NIV (Hilberg et al 1997; Mehta & Hill 2001; Ambrosino et al; Anton et al). For example, a study of 1033 patients conducted between 1998 and 2000 in a mixture of settings found that a GCS of ≤11 at baseline carried an OR of 4.40 for NIV failure and this increased to an OR of 5.16 if the GCS persisted at ≤11 at 2 hours into therapy (Confalonieri et al 2005). However, a relatively recent prospective observational study has challenged such viewpoints examining outcomes in 80 AHRF patients with a Glasgow Coma Scale (GCS) <8 (mean GCS 6.5; 11.6% of cases had a GCS of 3) where the impaired consciousness was felt to be specifically due to hypercapnic encephalopathy. The majority (66%) of these cases were due to COPD. In 85% of cases, the administration of NIV resulted in a complete recovery of consciousness (GCS improved to 15) and this took a mean time of 4.1 hours. NIV was considered to be a "success" in 80% of cases, this being defined by the authors as complete recovery of consciousness, discharge from ICU, and remaining alive and conscious on a hospital ward for at least 24 h without requiring resumption of NIV (Diaz et al 2005). Interestingly, an underlying diagnosis of COPD appeared to predict a better outcome from hypercapnic coma with NIV compared to other aetiologies e.g. pneumonia.

e) **Hyperglycaemia and metabolic dysfunction: Relevance as a prognostic marker in critically ill patients and in COPD exacerbations:** The presence of pre-therapy "baseline" hyperglycaemia has been shown to be an independent predictor of poor

outcome in critically ill patients. A study of 135 patients admitted to a Danish ITU found that the mortality of the 97 "surgical" patients (majority were post abdominal surgery) correlated with an increased blood glucose level as well as other factors i.e. APACHE 2 score on day 1 and 2 post ITU admission. A trend to increased mortality and blood glucose was found in the "medical" patient cohort (Christiansen et al 2004) but this did not reach statistical significance.

Hyperglycaemia has also been shown to portend an adverse outcome outside the context of ITU. In a study of 738 patients admitted to a Level 1 US trauma centre, the presence of "mild" (>7.5 mmol/l) hyperglycaemia carried a significantly elevated mortality (15.5 v 2%; $p<0.01$) as did "moderate" (>11.1mmol/l) hyperglycaemia (34.1 v 3.7%; $p<0.01$) (Yendamuri et al 2003). An analysis of 26 studies in patients with stroke showed that the unadjusted relative risk of in-hospital or 30 day mortality was 3.07 times higher in non-diabetic patients with relatively mild hyperglycaemia i.e. an admission glucose level between 6 and 8 mmol/L. This risk was greater than that seen in diabetic patients with the same blood glucose level (OR 1.30) (Capes et al 2001). A study examined the medical records of 2030 hospitalised patients admitted to a US teaching hospital with hyperglycaemia being defined as admission or in-hospital fasting blood glucose >7 mmol/l or a random blood glucose level ≥11.1 mmol/l on 2 or more occasions (Umpierrez et al 2002).

The prognostic value of hyperglycaemia in the context of COPD exacerbations has been documented in the literature. A retrospective case note review of 291 patients hospitalised with COPD exacerbations in a large UK teaching hospital found an increased mortality and longer hospital stay in patients with random blood glucose of 7mmol/l or more (Baker et al 2006). In this study, ICD-10 codes were used to identify 348 COPD exacerbations presenting to hospital over a 12 month period in the 291

subjects. Blood glucose values that were taken during the hospital admission were recorded. Only 5.3% of the cohort had a known diagnosis of Diabetes Mellitus. The median blood glucose value in the cohort was 7.0mmol/l with 72% of the cohort having a blood glucose level>6.1 mmol/l. Patients who died had a significantly higher mean blood glucose value (9.1 v 7.7 mmol/l; p=0.004). The mortality in the group where the blood glucose value was > 9mmol/l was 22% compared to just 11% in the group where the blood glucose level was <6.0mmol/l (12%; p=0.003). Furthermore, the risk of death was found to be increased by 10% for every 1 mmol/l increase in blood glucose. This study did not distinguish between the presence and absence of AHRF complicating the COPD exacerbations or the need for NIV. Little is known regarding the effect of hyperglycaemia in the context of NIV. One study looked at the role of "metabolic" complications associated with failure of NIV in the setting of COPD exacerbations. An Italian ITU based study conducted between January 1996 and May 1998 examined the factors associated with "late" failure of NIV i.e. where NIV is applied and this improves arterial pH/gas exchange but these parameters subsequently deteriorate 48 hours following the administration of NIV and whilst NIV is still being applied (Morretti et al 2000). In this study, NIV was being applied for a mean of 9.2 hours per day in the "late failure" group which amounted to 31 of the 137 patients studied (22.7%) in the total cohort comprising those who were initially treated successfully with NIV following admission with respiratory acidosis/AHRF. 19 of the 31 "late failures" were treated with endotracheal intubation and IPPV. The in-hospital mortality of the "late failure" group was 68%. The presence of "metabolic complications" (defined as hyperglycaemia) was found to be more frequent in the "late failures" i.e. hyperglycaemia was found in 7 of the "late failures" compared to 3 of the "successes" (22.5 v 3.8%; p=0.034). The presence of a

worse functional status defined by a lower Activites of Daily Living (ADL) score along with an increasing number of "complications" during the admission (i.e. pneumonia, sepsis, shock, renal failure, GI issues, cardiac impairment, coma etc) was also associated with "late failure" of NIV in this study. Neither age nor APACHE score appeared predictive of outcome in this cohort.

f) **Body Weight:** One study, albeit a retrospective analysis of 59 COPD admissions complicated by AHRF, found an association between being underweight and failure of NIV, a variable which had not previously been analysed in this context; the mean body weight was significantly higher at 69kg in the "NIV successes" compared to 48kg in the "NIV failures" ($p<0.01$) (Ambrosino et al 1995). Interestingly, since then, the issue of Body Mass Index has taken on a greater significance as a prognostic survival marker in COPD patients in general as part of the "BODE" index (Celli et al 2004) and further research into the role of BMI in the context of NIV is needed.

g) **Leak due to the interface or administration of excessive pressure support:** In contrast to endotracheal intubation and IPPV, a major source of asynchrony between the patient and the ventilator is that of leakage of the pressurized air delivered by the ventilator between the interface and the patient. In an early prospective case series charting the outcomes of 14 episodes of AHRF in 12 COPD patients treated with NIV via a "nasal" interface and volume cycled ventilators, the amount of "mouth leak" was noted to be significantly higher in the 7 NIV "failures" (314 v 100ml; $p<0.01$) (Soo Hoo et al 1994). 4 of the 7 NIV failures were noted to be edentulous in this study. However, in most acute settings these days, NIV is administered at least initially by a "full face" mask sealing the nose and the mouth rather than a "nasal only" interface. In the prospective survey of 42 ITUs conducted by Carlucci et al, 108 cases of acute respiratory failure were treated with NIV with 43 judged to have "failed". Tolerance

of NIV and air leak was measured using a semi-quantitative scoring system (Carlucci et al 2001). Only 9% of the NIV successes were deemed to have "large" air leaks compared to 28% of the NIV failures ($p<0.004$) and poor tolerance of NIV was a significant predictive factor of success or failure following multivariate analysis. Interestingly in this study, the use of a "facial" or "nasal" interface was not predictive of success or failure of NIV.

A prospective observational analysis of 60 patients receiving acute NIV found that 43% exhibited what the authors defined as "severe" patient-ventilator asynchrony (an asynchrony index >10% of all breaths) (Vignaux et al 2009). Following multivariate analysis, the presence of mask leak emerged as a predictor of the presence of "severe" patient-ventilator asynchrony along with an increasing amount of pressure support that in fact may be linked to the degree of leak. The study found that patient comfort (measured by a VAS scale) declined with an increasing amount of asynchrony observed. The presence of excessive leak was perceived by the ventilator as an inspiratory effort by the patient resulting in the delivery of a breath, so called "auto-triggering"; this was seen in 13% of cases and recognised by clinicians as a "spiked" positive deflection on ventilator waveform analysis. Leak from the mask was also found to cause the ventilator to continue to give a breath in when patient was trying to breathe out, so called "delayed cycling"; this was seen in 23% of cases and recognised by clinicians as a continuous plateau flat shaped curve with a secondary positive deflection continuing when the inspiratory flow had dropped off. However, data is needed which measures clinical outcomes such as mortality and need for intubation as a specific consequence of the phenomena described above and whether reduction of these phenomena by altering the ventilator settings improves these clinical outcomes and tolerance of NIV.

h) **Lung Function:** Only 2 studies have shown a relationship between lung function when stable and outcome from NIV when acutely unwell but with conflicting results. Anton et al conducted an observational study of 44 episodes in 34 patients treated with NIV for AHRF where 10 episodes did not respond to NIV (Anton et al 2000). Interestingly, the FEV1 in the "failure" group was significantly higher when compared to the "success" group (38% predicted v 27% predicted) but the FVC was no different implying a more severe level of airflow obstruction in those who succeeded. In contrast, an earlier study conducted in 47 COPD patients with 59 episodes of AHRF undergoing NIV. In the 22% who failed NIV, FVC was significantly lower compared to the NIV successes (0.9 v 1.6 litres; $p<0.05$) although this data was only available in 2/3 of cases (Ambrosino et al 1995).

i) **Airway colonization and antibiotic therapy prior to NIV:** The presence of Pseudomonas Aeruginosa colonising the airways of patients with COPD have been shown to lead to reduced quality of life and increased exacerbations but little is known regarding its relevance specific to NIV (Murphy et al 2008). Ferrer at al studied 86 COPD patients with AHRF requiring NIV prospectively over a 2 year period with 22 "failing" NIV. None had evidence of pneumonia clinically or radiologically at presentation. The presence of airway colonization (obtained from tracheal aspirates) with non-fermenting Gram negative bacteria i.e. pseudomonas aeruginosa was significantly associated with failure of NIV (OR 5.16; $p=0.016$). Interestingly, an increased use of antibiotic therapy *prior* to admission was also linked to failure of NIV (OR 5.1; $p=0.006$) along with an APACHE 2 score >16 (Ferrer et al 2005).

j) **Heated Humidification:** Considerable uncertainty exists as to whether the practice of humidifying inspired air during acute NIV offers any advantage to the patient let

alone attempting to define what level of adequate humidification should be required in order to maximize outcomes in NIV. The lack of data regarding NIV is amplified by the fact that the levels of humidity thought to be relevant for IPPV (where the upper airway is bypassed by the endotracheal tube; a figure suggested at 30 mgH2O/L) cannot be applied to NIV where the upper airway, a "natural humidifier" is not bypassed (Ricard et al 2009). A number of different systems have been studied with respect to how humidification is delivered in NIV. Humidification using a "Heat and Moisture Exchanger" (HME) has been shown to increase the work of breathing and have a detrimental impact during acute NIV when compared with using a "Heated Humidifier" (HH) system (Lellouche et al 2002; Jaber et al Intensive Care Medicine 2002). However, a recent randomised controlled trial has failed to show that in NIV, such physiological consequences of HME humidification translates into worse outcomes clinically such as an increased mortality rate or need for intubation; in fact it was the HH system which fared worse in this respect (Abstract form only to date; Lellouche et al 2005). Clearly, further research into this important area is needed.

1.17 Attitudes of COPD patients towards Ventilatory Support and Advanced Directives of Care

NIV is increasingly being offered to COPD patients presenting to hospital with respiratory acidosis as it has now become a standard of care in managing acute hypercapnic respiratory failure. In 2003, a UK National COPD audit comprising 94% of UK hospitals and 7529 COPD patients reported that NIV was administered to just 31% of patients exhibiting a respiratory acidosis (Kaul et al 2009). However, just 5 years following this study, the 2008

UK National COPD audit gathered data from 9716 COPD patients and showed that 70% of patients with respiratory acidosis noted either at presentation to hospital or at some point during their admission were treated with NIV (Roberts et al 2011). Furthermore, data from the literature serve to challenge some commonly held misconceptions held by some healthcare professionals about the value of endotracheal intubation and instituting IPPV during acute exacerbations of COPD. Such misconceptions may stem from a belief that COPD patients exhibit ''ventilator dependency'' and will invariably sustain a poor outcome when invasively ventilated. In a study of 74 patients admitted to the ITU with acute respiratory failure secondary to COPD, 85% underwent endotracheal intubation and IPPV (Breen et al 2002). The mean APACHE 2 score of the group was high at 22 with a high baseline PaCO2 of 12.0kPA prior to IPPV thus representative of a truly critically ill cohort. Prior to hospital admission, 40.5% of patients were classified as being "housebound" by the authors. The mean period of IPPV was 3.2 days and only 13% of the cohort needed ventilatory support for longer than a week. 80% survived to discharge with the 1 year mortality rate of the whole study population being 48.6%. Interestingly, the 1 year mortality rate of this cohort was not dissimilar from a cohort of 110 COPD patients who had survived an episode of AHRF after being treated with NIV where 49.1% had died 1 year post discharge (Chu et al 2004). In a retrospective review of 166 COPD patients requiring IPPV, the in-hospital mortality was only 12% in those COPD patients with no other comorbidities and 28% for the whole cohort. The mean duration of time spent on the Ventilator for the group was 8.9 days (Nevins et al 2001). However, in these studies, NIV was not widely available which may not be representative of modern day practice where IPPV is usually offered to patients who either fail or are not deemed suitable for a trial of NIV first. Despite the evidence above, the 2008 UK COPD audit revealed that of all the COPD patients with

AHRF receiving NIV, only 3.2% of patients receiving NIV had their care escalated and received IPPV (Roberts et al 2011) and only 1% of the overall cohort received IPPV.

In modern clinical practice, any decision to institute either NIV or IPPV in COPD exacerbations must take into account the patient's wishes and respect the autonomy of the individual. Often, such decision making is done during the exacerbation itself (SUPPORT study 1996; McNeely et al 1997). Such a scenario leaves little time for informed decision making by physicians, patients and carers alike. Thus, it may be preferable to address "End of Life" issues in the outpatient setting when patients are clinically stable. A survey of 279 respiratory physicians in Canada found that 84% undertook discussions on mechanical ventilation only after their patients became severely breathless (84%) and three quarters did so when the FEV1 fell to below 30% of predicted. The same survey found that 43% of the physicians discussed these issues only during an exacerbation that actually required the need for mechanical ventilation (McNeely et al 1997). Little is known regarding COPD patient attitudes, beliefs and preferences for ventilatory support and end-of-life care, particularly in the UK. In COPD, what data is available suggest that the majority of patients feel that end of life issues ought to be discussed with healthcare professionals on a routine basis (Gaber et al 2004; Curtis et al 2004; Knauft et al 2005). In a US study surveying 40 COPD patients, only 14% had previously discussed the issue of mechanical ventilation (Travaline et al 1995). In another US study, in a cross sectional analysis of 100 patients with chronic lung conditions (over half the sample having obstructive lung disease), 85% stated an interest in having end of life discussions with their doctors yet only 21% of the sample reported actually having had such discussions previously (Pfeiffer et al 2003). These findings were mirrored in a UK outpatient based study interviewing 100 COPD patients where 75% felt that end of life discussions ought to be undertaken (Gaber et al 2004).

Considerable variability exists in the literature in the proportion of COPD patients opting to receive life sustaining treatments such as CPR and/or mechanical ventilation. Gaber et al found that of 100 UK COPD patients interviewed, 48% wished for "all treatments" i.e. NIV, IPPV and CPR; 19% wished for IPPV and NIV but not for CPR and only 12% declined all 3 interventions (Gaber et al 2004). 54% of this study population had an FEV1 <40% of predicted, 24% were using LTOT and 56% had one hospital admission in the preceding 12 months perhaps representative of a population who may one day need to partake in such a process outside the context of research. An earlier US study of 40 COPD patients (ranging in severity with FEV1 between 0.29-2.64 litres) found that only 40% of the sample wished to receive IPPV during an exacerbation. A preference for NIV was not surveyed in this paper (Travaline et al 1995). Another US study conducted between 1999 and 2002 interviewing 101 COPD patients (mean FEV1 26%, all using home oxygen) found that 62.2% of the sample would want IPPV while 63.6% would wish for CPR in the event of an exacerbation (Stapleton et al 2005). Variability has been also shown in physicians' decision making when withholding or withdrawing life sustaining treatment in their COPD patients (Perrin Clinical Med 2003; Wildman et al 2003). In a UK based survey, 120 Consultants were given 3 hypothetical scenarios where they were asked to admit a COPD patient to ITU following a failed trial of NIV based on a "2am telephone conversation with their registrar" and were also asked to estimate the chances of each patient surviving the episode (Wildman et al 2003). For scenario 1, only 3% of Intensivists would choose not to admit the patient to ITU compared to 17% of other non-respiratory physicians and the predicted chances of ITU survival given by Consultants ranged from 33 to 56%. The variability observed in the decision making of both physicians and patients regarding attitudes to life sustaining treatments might suggest that this group could benefit from decision making aids in order to make informed choices regarding their care. The potential utility for validated decision aids in this setting is heightened by

studies which show that the information given to patients by their physicians regarding life-sustaining therapies may be modified in order to influence the decision (a process known as "framing") (Mcneely et al 1997; Sullivan et al 1996). This modification has been shown to occur based on what the physician's expectation and perception may be for their patient's chances of survival and quality of life respectively, an area which has been shown to suffer from considerable subjective variability (Wildman et al 2003; Wilson et al 2000; Uhlmann et al 1991). The impact of decision aids has not been extensively studied in the literature in respect of COPD despite the incidence and impact on mortality and hospital admissions. In one US study, the use of a decision aid concerning IMV resulted in an increase in the proportion declining IMV from 50% to 60% and only 2 of 18 patients interviewed 12 months later had actually changed the initial decision made following the use of the aid (Dales et al 1999).

Severe COPD is an advanced progressive and as yet incurable disease. Data from the SUPPORT study, conducted in 5 tertiary US centres, found that when comparing patients with advanced lung cancer and COPD who had died in hospital, those with COPD were much more likely to have undergone mechanical ventilation (70.4% v 19.8%). Furthermore, severe dyspnoea occurred in 56% of the COPD cohort compared to 32% of the lung cancer group (Claessens et al 2000). These findings were echoed in a study from the UK which compared 50 patients with COPD to 50 patients with inoperable Non-Small Cell Lung Cancer (Gore et al 2000). The COPD arm scored significantly higher scores for all but 2 components of the 9 item SF-36 health status measure and was also significantly more functionally limited when compared to the Lung Cancer cohort. Furthermore, whilst the majority of the Lung Cancer cohort felt able to accept the diagnosis and retain a fairly positive outlook but most of the COPD cohort patients expressed frustration and anger at the symptoms also displaying clinically relevant anxiety and depression scores; the latter finding not seen in the cancer

cohort. Despite this data, whilst 30% of the Lung Cancer cohort received specialist palliative care support, none of the COPD group received it.

1.18 The unmet need for End of Life Care in COPD patients: The Department of Health End of Life Care Strategy and Advanced Care Planning

In 2008, in response to such findings, the Department of Health published the End of Life Care Strategy which recognised that despite 58% of all deaths occurring in hospital, patients may not receive optimal symptom control and furthermore, patient and carer involvement in End of Life decision making was often found to be lacking *(Department of Health. End of life care strategy: promoting high quality care for all adults at the end of life. Department of Health 2008)*. A particular problem identified in the Department of Health report relating to acute hospital End of Life care was a failure of clinicians to recognise when continuation of treatment was not in the best interests of the patient. Thus, preferences regarding mechanical ventilation should be an integral part to "End of Life" discussions in COPD. The report also comments that "Advance Care Planning" is a helpful way of eliciting patients' preferences regarding the type of care they would wish to receive and furthermore mentions that this could be achieved by the completion of a statement of the person's wishes and preferences regarding future care or an advance decision to refuse specific treatment. Despite these recommendations arising from this report, there is very little data previously exploring the uptake of Advanced Directives of Care (ADCs) in COPD populations from the United Kingdom contrary to that seen in the US (Heffner et al 1997; Llovera et al 1999). Furthermore, it would be of interest to determine whether any association exists between commonly measured variables such as health status, pulmonary function and capacity to perform activities of daily living (ADLs) with patient willingness to discuss End of Life

issues, preferences for life sustaining therapy and interest in framing ADCs . Such findings may give further insight into the ''thinking'' behind the decision making of COPD patients regarding end-of-life issues.

1.19 Overview of this thesis

This thesis aims explores aspects relating to the epidemiology, diagnosis and management of COPD both in the industrialised developed world and the rural developing world. COPD continues to be a significant burden to the healthcare system of developed world countries and a large proportion of this burden is seen through the impact of acute exacerbations of COPD resulting in hospital admission. The thesis comprises 3 original studies covered in Chapters 2, 3 and 4. Chapter 2 describes a study exploring which baseline variables, recorded at the bedside by clinicians, may predict the outcome when Non Invasive Ventilation is administered in decompensated ventilatory failure complicating COPD exacerbations and specifically whether the presence of hyperglycaemia is associated with an increased likelihood of failure of Non Invasive Ventilation in such a setting. Given that COPD is a chronic progressive, incurable disease and that a not insignificant proportion of individuals fail to recover from an episode of decompensated ventilatory failure, the study described in Chapter 3 of this thesis goes on to explore the attitudes of COPD patients to receive Ventilatory support and End of Life Care and examines which variables, when assessed in the stable state, predict the willingness of COPD patients to receive life sustaining treatments as well as exploring the awareness and uptake of Advanced Directives of Care in a UK urban COPD population. Chapter 4 takes the reader back to some of the key themes addressed in this Chapter. This study described in chapter 4 aims to better understand the incidence of COPD in a rural developing world region i.e. India which will bear a significant burden of the

disease in generations to come but where presently little data exists in the literature regarding epidemiology, lung function or which variables and exposures increase the risk of persons developing COPD. Chapter 5 summarises the key messages emerging from the studies highlighted in the Chapters 2 to 4 as well as discussing areas for further research in these fields.

1.20 Aims of this thesis

Non Invasive Ventilation during acute exacerbations of COPD: *We know how to do it but do we know how to do it well?*

- ***Does the presence of baseline hyperglycaemia predict an adverse outcome from NIV?*** It is apparent from studies of "real world" data that NIV is now being offered in the acute setting to COPD patients who are "sicker", exhibit greater physiological derangement and present with more severe degrees of respiratory acidosis than those observed in some the early clinical trials. However, what is also clear is that NIV may fail to improve clinical outcome in a significant proportion of patients admitted with acute hypercapnic respiratory failure. Whether those same "risk factors" that emerged from the earlier studies that appeared to predict failure of NIV still operate today and to the same degree is not clear. Furthermore, whether hyperglycaemia upon presentation, often seen as an adverse prognostic marker in other acutely ill patient groups, influences the outcome of NIV in acidotic COPD patients is not known nor is its relationship to other identified predictors of outcome. This is the subject of Chapter 2.

- ***Which variables predict willingness of COPD patients to accept Ventilatory support and what is the awareness and uptake of advanced directives of care in COPD patients?*** Ventilatory support is increasingly being offered to COPD patients presenting to hospital with acute respiratory acidosis. However, any decision to institute ventilatory support in COPD exacerbations must take into account patient's wishes and respect the autonomy of the individual. Little is known regarding COPD patient attitudes, beliefs and preferences for ventilatory support and end-of-life care in the UK and whether any association exist between the willingness of patients to receive ventilatory support and commonly measured variables such as health status, pulmonary function and capacity to perform activities of daily living (ADLs). It would also be of interest to measure the impact of decision aids to facilitate informed choices regarding life sustaining therapy and better understand the awareness and uptake of Advanced Directives of Care (ADCs) among COPD patients in the UK. This forms the subject of Chapter 3.

Risk factors for the development of COPD in rural India: *The significance of being underweight?*

- **Chronic airflow limitation in a rural Indian population: Aetiology and relationship to body mass index:** Clinicians caring for patients in rural developing world settings may often lack ready access to reliable lung function testing in order to make an accurate diagnosis of COPD hence surrogates predicting the diagnosis of COPD in a patient become more relevant in such regions. The need for such surrogates is heightened particularly when the literature from developing world countries suggests that exposure to factors other than tobacco may place individuals at higher risk of airflow obstruction. From a clinical and epidemiological perspective, it

would also be of future interest to determine whether modifying those risk factors identified with the development of airflow obstruction in rural developing world settings e.g. such as being underweight would lead to a decrease in the overall prevalence of COPD and severity of airflow obstruction in the population studied. Furthermore, it would be of interest to better understand the risk factors associated with the development of COPD in such settings and whether such risk factors differ from those found in the developed world.

Chapter 2: Hyperglycaemia as a predictor of outcome during Non-Invasive Ventilation for COPD exacerbations complicated by decompensated ventilatory failure

2.1 Introduction

Non-invasive ventilation (NIV) is an effective treatment for acute hypercapnic respiratory failure (AHRF) complicating a COPD exacerbation (Lightowler et al 2003). However, some patients do not improve with NIV and in these individuals Invasive Positive Pressure Ventilation (IPPV) or, where appropriate, palliation, are needed. NIV is now offered to COPD patients presenting with more severe acidosis than in these early clinical trials and still appears to be just as effective in improving clinical outcomes (Carlucci et al 2003). Whether the same risk factors operate and do so to the same degree is not clear.

In patients with a wide range of conditions admitted to intensive care pre-therapy hyperglycaemia is an independent predictor of a poor outcome (Christiansen et al 2004; Capes et al 2001; Umpierrez et al 2002; Yendamuri et al 2003) which may be improved by tight glycaemic control (Van den Berghe G et al 2001; Van den Berghe G et al 2006). A retrospective case note review of patients hospitalised with COPD exacerbations but not necessarily exhibiting respiratory failure found an increased mortality and longer hospital stay in patients with random blood glucose of 7mmol/l or more (Baker et al 2006). Whether hyperglycaemia upon presentation influences the outcome of NIV in acidotic COPD patients is not known nor is its relationship to other identified poor prognostic factors. To investigate these relationships we prospectively collected data about the occurrence of hyperglycaemia and the risk factors identified above in an observational study of consecutive COPD patients undergoing NIV.

2.2 Methods

2.2.1 Patients

All patients admitted to University Hospital Aintree between June 2006 and September 2007 with an exacerbation of COPD who received NIV within 24 hours of admission to the Respiratory Failure Unit (RFU) or ICU were prospectively identified. AHRF was defined by the presence of worsening of dyspnoea and an arterial pH<7.35 with a PaC02 >6kPa. The diagnosis of COPD was made clinically and confirmed by spirometry whenever possible (Rabe et al 2007). Where spirometry was unavailable, a senior respiratory clinician i.e. at Consultant level confirmed that COPD was the most likely diagnosis based on the history, tobacco exposure, examination findings and radiology. An exacerbation of COPD was defined according to pre-existing criteria (Rabe et al 2007) while pneumonia was diagnosed when a new infiltrate on the chest radiograph occurred with one or more of the following: dyspnoea, cough, sputum production, fever greater than >38 degrees, abnormal breath sounds and rales (Bartlett et al 1998). We excluded patients with other respiratory conditions e.g. chest wall and neuromuscular disease leading to acute on chronic ventilatory failure, those presenting with acute cardiogenic pulmonary oedema, those patients where doxapram was used as an adjunct to NIV, patients commenced on NIV >24 hours following hospital admission, those with known active malignancy or a diagnosis of acute or chronic thromboembolic disease. In addition, COPD patients weaned using NIV post-extubation and those unable to tolerate the mask due to agitation or claustrophobia were excluded.

2.2.2 Protocol for administration of NIV complicating acute hypercapnic respiratory failure

In our institution, emergency admissions presenting with acute exacerbations of COPD and community acquired pneumonia are managed based on national guidelines *("BTS guidelines*

for the management of chronic obstructive pulmonary disease. The COPD Guidelines Group of the Standards of Care Committee of the BTS." 1997; "Non-invasive ventilation in acute respiratory failure." 2002 57(3): "2004 update of BTS pneumonia guidelines: what's new?").

Hypercapnic respiratory failure complicating acute exacerbations of COPD is managed with a regimen of controlled oxygen, nebulised bronchodilators, corticosteroids with antibiotics and diuretics if indicated whilst the decision to administer intravenous theophyllines is left to the judgement of the admitting clinician. Arterial blood gas (ABG) analysis is performed immediately on admission with the presence of persisting/worsening respiratory acidosis (defined as pH>7.35 and PaCO2>6 kPa) following 1 hour of "medical management" and controlled oxygenation being an indication to administer assisted ventilation. However, NIV may also be administered earlier at the discretion of the admitting team should the clinical circumstances dictate e.g. hypercapnic coma in a patient where IPPV is deemed inappropriate etc.

All patients admitted to our hospital with acute respiratory failure requiring NIV are managed either in a specialised Respiratory Support Unit (RSU) under the direct supervision of a Consultant Respiratory physician or in a 12 bed Intensive Care Unit (ICU). The RSU consists of a 8 bed unit with a dedicated nurse per 2/3 patients trained in the administration of respiratory support including application of NIV and tracheostomy care. The decision to administer NIV is discussed with a Consultant Respiratory physician in all cases prior to administration. For those patients requiring assisted ventilation in A&E, NIV is administered by means of a BiPAP Synchrony© ventilator by a trained physiotherapist whilst awaiting transfer to the RSU or ICU. Upon transfer to the RSU, a BiPAP Vision© ventilator device is used. The respiratory rate is recorded by a physician prior to initiation of NIV. Ventilator

settings are adjusted according to patient comfort, oximetry and arterial blood gas values whilst ABGs performed at 1 hour and 4 hours post NIV initiation in all patients according to local protocol. At initiation of NIV, starting pressures of 10 cm H20 (Inspiratory) and 4 cm H20 (expiratory) are used and subsequently titrated upwards according to clinical response. Regarding the ventilator-patient interface, a full face mask is used both in the RSU and in ICU. Patients were encouraged to use NIV for as much as possible during the first 24-48 hours subsequent to initiation and period of use thereafter at the judgement of a Consultant Respiratory physician based on clinical circumstances. All patients are monitored continuously in terms of pulse oximetry and cardiac rhythm during the period of assisted ventilation. In all cases a ceiling of treatment based on the patients' clinical condition, patient wishes and those of their carers was agreed with the physicians and intensivists responsible for the care at the time treatment began. Prior to commencement of NIV, informed verbal consent is obtained in conscious patients displaying no impairment of cognition.

2.2.3 Study Protocol and measurements

Before initiating NIV, the respiratory rate was measured by a physician together with the arterial blood gases which were repeated at 1 and 4 hours post-treatment. Details of the diagnosis, associated co-morbidities, usual medication including oral corticosteroids, previous lung function and the time from presentation to the initiation of NIV were recorded together with body temperature, haemodynamic status and Glasgow Coma Score (GCS) pre-NIV. Venous blood was drawn for the measurement of the blood count (Sysmex XE-2100 automated full blood count analyser; Sysmex© Milton Keynes, UK), routine biochemistry (AU 2700 automated chemistry analyser; Olympus©) and random glucose levels (Hexokinase method, AU 2700 Olympus©). In all episodes, blood samples were taken on

admission to the Emergency Department but before NIV began i.e. the first blood glucose value that was obtained on hospital arrival was used. Hyperglycaemia was defined as a random blood glucose level ≥ 7mmol/l (Baker et al 2006). The baseline Acute Physiology and Chronic Health Evaluation (APACHE II) score was calculated by a single investigator (B.C) (Knaus et al 1995). Pre- admission co-morbidity was assessed using the Charlson Co-morbidity index (Charlson et al 1987).

2.2.4 Definition of Successful NIV in the study

Successful NIV was defined as the resolution of respiratory acidosis leading to successful weaning from the ventilator, and no requirement for ventilatory support for at least a further 48 hours. Formal ethical approval for the study was obtained via the regional ethics committee.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 15.0. Data are presented as mean and standard deviation unless otherwise stated. We used the independent sample t-test to identify significant differences in continuous variables between patients failing or succeeding with NIV and the chi-squared test for categorical variables. Statistical significance was defined as a p value <0.05. No "a priori" power calculation was performed as the relationship between blood glucose and NIV success in COPD patients was not known. The statistical significance of each variable, in predicting the outcome from NIV was initially determined using univariate logistic regression. Subsequently, baseline variables with a p value < 0.1 were included in a multivariate logistic regression model which identified the most parsimonious predictors of NIV outcome. The variables identified from the logistic regression model were used to construct receiver –operator curves (ROC) from which we determined the sensitivity,

specificity, positive and negative predictive value of these factors. Candidate variables were considered in isolation and in combination to establish whether they added additional explanatory power to this analysis.

2.4 Results

Of 168 patients receiving NIV for decompensated AHRF, 109 episodes in 92 patients fulfilled the study entry criteria. 2 patients were excluded due to claustrophobia and agitation during treatment leaving 107 episodes in 90 patients. Thirteen patients presented with more than one episode of AHRF during the study period comprising 17 such episodes in total. For those patients presenting with more than one episode of AHRF during the study period, the 1st episode was used for the purposes of the study leaving 90 episodes in 90 patients. Random blood glucose data were available in 88 of these 90 patients thus leaving 88 episodes in 88 patients for final analysis.

The ceiling of treatment was set at NIV alone in 73% (64/88) of patients. NIV failed in 16 patients (18%), one patient who received invasive ventilation surviving to discharge while the remaining 15 patients died, all of whom had NIV as their ceiling of treatment. In 11 (12%) patients, COPD exacerbation was associated with pneumonia but the mortality was not worse in this subgroup (p=0.12). NIV was administered in the RFU in 86 patients and in ICU for the remaining 2.

The baseline demographics of the study population are outlined in table 1.

Table 1: Baseline demographics of study population

Variable	Value
Age (years; mean & SD) *n=88*	70 (10)
Gender *n=88*	39=male (44%) 49=female (56%)
FEV1 (litres; mean & SD) *n=82*	0.68 (0.29)
FVC (litres; mean & SD) *n=82*	1.62 (0.56)
Known diagnosis of diabetes mellitus	Yes=16 (18%; 4 prescribed insulin) No=72 (82%)
Glucose level prior to NIPPV initiation *n=88*	0-6.9mmol/l=44 (50%) >7mmol/l=44 (50%)
Arterial pH prior to NIPPV initiation (mean & SD) *n=88*	7.25 (0.64)
Arterial pCO2 prior to NIPPV initiation (kPa; mean & SD) *n=88*	10.20 (2.17)
Arterial pO2 prior to NIPPV	8.19 (2.65)

initiation (kPa; mean & SD) *n=88*	
Calculated Bicarbonate (mmol/l; mean & SD) *n=88*	25.65 (3.60)
Respiratory Rate prior to NIPPV initiation (breaths per minute; mean & SD) *n=88*	27 (8)
APACHE II score prior to NIPPV initiation (mean & SD) *n=88*	15 (4)
Charlson co-morbidity index (mean & SD) *n=88*	1.66 (0.76)

Spirometry data confirming the diagnosis of COPD were available for 82 (93%) patients, all recordings being within a year of the index admission.

The 6 cases where COPD was diagnosed clinically without spirometry are detailed below:

- 4 cases: Diagnosis of COPD made in primary care, patient established on inhaled bronchodilators, presentation with AHRF resulting in death in all 4 cases; diagnosis

- 2 cases: Diagnosis of COPD made in secondary care, patient established on inhaled bronchodilators, unable to perform valid spirometry due to severe dementia; 1 of the 2 cases survived to discharge

2 of these 6 cases presented with pneumonia.

In 16 patients (18%), oral corticosteroids were taken before admission. Intravenous aminophylline was administered in 24 patients and this did not affect the outcome of NIV (3 NIV failures received aminophylline p=0.54; non-significant).

2.4.1 Glycaemia and outcome of NIV

The relationship between hyperglycaemia and outcome from NIV is summarized in table 2. Hyperglycaemia was present at baseline in 50% (44/88) of patients whilst 16 (18%) had a pre-existing diagnosis of diabetes mellitus. NIV failure was seen in 34% (15/44) of patients where random blood glucose was ≥7mmol/l compared to 2% of the group with blood glucose ≤ 6.9 mmol/l (1/44; p=0.003). The mean blood glucose level was higher in patients when NIV failed (9.03 (3.22) mmol/l v 7.01 (2.18) mmol/l; t test; p=0.003).

In 72 patients, oral corticosteroids were not taken before hospital admission and NIV succeeded in 58. In this sub-group, baseline hyperglycaemia was present in 38% (22/58) of NIV successes and 93% (13/14) of NIV failures (p<0.001). Hyperglycaemia was not related to prior oral corticosteroid use. Of the 16 patients prescribed oral corticosteroids pre admission, 9 (56%) presented with hyperglycaemia compared to 35 of 72 (49%) not prescribed oral corticosteroids (p=0.59; non significant).

Table 2: Relationship between glycaemia and outcome from NIV

Random blood glucose quartile (mmol/l)	NIV success (no of cases)	NIV failure (no of cases)
0-6 *(n=28)*	27 (96%)	1 (4%)
6-6.9 *(n=16)*	16 (100%)	0 (0%)
7-8.9 *(n=26)*	17 (65%)	9 (35%)
>9 *(n=18)*	12 (67%)	6 (33%)

A prior diagnosis of diabetes mellitus pre admission was not associated with failure of NIV (see table 3) with the mean blood glucose in the 16 diabetic patients being 8.03 (4.02) mmol/l compared to 7.23 (2.04) mmol/l in non-diabetics (p=0.25 non significant). Of the 44 patients with hyperglycaemia, pneumonia was noted in 7 (16%) compared with 4 patients (9%) with normoglycaemia (p=0.52 non significant).

When taking only those 82 patients where the diagnosis of COPD was confirmed by spirometry, the association between hyperglycaemia and failure of NIV remained. In this sub-group, NIV was successful in 71 patients and failed in 11. Baseline hyperglycaemia was present in 41% (29/71) of NIV successes and 100% (11/11) of NIV failures ($p<0.001$).

2.4.2 Arterial blood gases and outcome of NIV

The relationships between the baseline pH, subsequent change in arterial blood gases over 4 hours and outcome of NIV are shown in tables 4. A baseline pH < 7.30 before NIV did not

predict NIV failure, although the relationship between outcome and presentation with a baseline pH below 7.25 approached statistical significance (p=0.09). In 84 patients, NIV was still being used 4 hours after initiation (4 patients had died by this stage). Failure to improve arterial pH compared to baseline after 4 hours NIV treatment was not associated with treatment failure nor was the inability to normalize pH following 4 hours of NIV predictive.

Table 3: Clinical variables and outcome from NIV- univariate analysis

	NIV success (n=72)	**NIV failure (n=16)**	**Odds Ratio**	**95% CI**	**P value**
Age (mean & SD)* *n=88*	68 (10)	77 (9)	0.9	0.84-0.97	p=0.006
Gender† *n=88*	M=34 F=38	M=5 F=11	1.97	0.62-1.97	p=0.25 (NS)
Smoking status† *n=88*	ex=37 current=35	ex=10 current=6	0.57	0.19-1.72	p=0.32 (NS)
FEV1 (litres; mean & SD)* *n=82*	0.69 (0.30)	0.60 (0.17)	4.53	0.19-106.4	p=0.35 (NS)
FVC (litres; mean & SD) * *n=82*	1.67 (0.55)	1.35 (0.48)	3.64	0.73-18.07	p=0.11 (NS)
Diagnosis of Diabetes Mellitus†	12	4	0.6	0.17-2.18	p=0.44 (NS)

n=16					
Glucose ≥ 7 mmol/l† *n=88*	Glucose≥7mmol/l=29 Glucose<7mmol/l=43	Glucose≥7mmol/l=15 Glucose<7 mmol/l=1	0.05	0.006-0.36	P=0.003
Time from admission to NIPPV administration (hours; mean & SD)* *n=88*	4.68 (4.76)	3.59 (3.85)	1.07	0.92-1.24	p=0.40 (NS)
IPAP (cmH2O; mean & SD)* *n=88*	15.07 (2.17)	15.00 (3.29)	1.01	0.80-1.28	0.34 (NS)
EPAP (cmH2O; mean & SD)* *n=88*	5.24 (1.38)	5.63 (1.78)	0.84	0.58-1.2	0.16 (NS)
APACHE II (mean & SD)* *n=88*	14.63 (3.80)	19.19 (4.31)	0.76	0.65-0.89	P=0.001
Oral Corticosteroid administered prior to	14 (19%)	2 (13%)	1.69	0.34-8.31	0.52 (NS)

admission † *n=16*					
Charlson co-morbidity index (mean & SD)* *n=88*	1.62 (0.73)	1.88 (0.93)	0.78	0.35-1.25	0.20 (NS)
GCS (mean & SD)* *n=88*	14 (1)	13 (3)	1.21	0.93-1.45	p=0.18 (NS)
Pneumonia cases† *n=11*	7	4	0.32	0.08-1.28	p=0.12 (NS)
Baseline RR (bpm; mean & SD)* *n=88*	26 (6)	34 (10)	0.86	0.79-0.94	P=0.001

*T test

†Chi squared test

Table 4: Outcome from NIV and relationship with arterial blood gas variables - univariate analysis

	NIV success (n=72)	**NIV failure (n=16)**	**Odds Ratio**	**95% CI**	**P value**

Baseline pH (mean & SD)* *n=88*	7.26 (0.06)	7.22 (0.08)	3.96	1.55-5.07	p=0.02
Baseline Pa02 (kPA; mean & SD)* *n=88*	8.15 (2.73)	8.30 (2.31)	0.98	0.80-1.20	p=0.87 (NS)
Baseline PaCO2 (kPA; mean & SD)* *n=88*	10.20 (2.19)	10.20 (2.16)	0.99	0.78-1.28	p=0.99 (NS)
Baseline calculated bicarbonate (mmol/l; mean & SD)* *n=88*	26.09 (3.44)	23.51 (3.69)	1.24	1.04-1.45	P=0.014
1 hour pH* (mean & SD) *n=88*	7.29 (0.06)	7.25 (0.09)	1.78	0.04-2.23	p=0.03
1 hour PaCO2 (kPA; mean & SD)* *n=88*	8.84 (2.21)	9.50 (2.61)	0.88	0.68-1.15	p=0.36(NS)
1 hour PaO2 (kPA; mean & SD)*	8.77 (2.87)	7.85 (1.64)	1.27	0.84-1.91	p=0.26 (NS)

n=88					
4 hour pH* (mean & SD)* *n=84*	7.32 (0.51)	7.28 (0.90)	4.34	2.90-5.89	P=0.14 (NS)
4 hour PaO2 (kPA; mean & SD)* *n=84*	8.37 (2.39)	7.70 (1.22)	1.27	0.79-1.96	p=0.31 (NS)
4 hour PaCO2 (kPA; mean & SD)* *n=84*	8.19 (1.98)	8.47 (2.07)	0.93	0.68-1.27	p=0.66 (NS)

* T test

2.4.3 Logistic Regression Analysis

Of the baseline variables tested, age, blood glucose < 7mmol/l, baseline respiratory rate, APACHE II score, mean baseline arterial pH pre-NIV and calculated serum bicarbonate level were related to the outcome of NIV treatment in the uni-variate logistic regression (see tables 3&4). These variables were included in the multivariate model which identified 3 statistically significant predictors of NIV outcome: baseline Respiratory Rate (OR 0.91; 95% CI 0.84-0.99), random glucose ≥ 7 mmol/l (OR 0.07; 95% CI 0.007-0.63) and, APACHE II score on admission (OR 0.75; 95% CI 0.62-0.90). The model correctly classified 93% of the successful outcomes in the sample.

Statistically significant correlations were noted between blood glucose concentration, respiratory rate and pre-NIV pH in those patients where NIV was successful and with baseline APACHE II score and pre-NIV pH where NIV failed. The correlations between

baseline RR and APACHE II index and with Pre-NIV pH were 0.25 (p=0.01) and -0.16 (p=0.14 NS) respectively in the whole cohort.

To further investigate the discriminatory power of the three variables, receiver operating curves (ROC) were constructed between RR, APACHE II index, blood glucose level and the outcome of NIV. For baseline RR and NIV outcome, the lines for sensitivity and specificity intersected at RR of 30 per minute (area under curve 0.78; 95% CI 0.62-0.94). In terms of APACHE II index, the point of intersection occurred at 16.5 (area under curve 0.79; 95% CI 0.66-0.91) and with random blood glucose level (area under curve 0.76; 95% CI 0.63-0.89) the point of intersection was at 7.3 mmol/l. The sensitivity, specificity, positive and negative predictive value of these factors in predicting a successful outcome is shown in table 4.

Table 4: Sensitivity, specificity, positive and negative predictive value of RR, glycaemia and APACHE 2 index in predicting outcome of NIV

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
RR<30/minute n=65; success=61 (94%)	82%*	75%*	94%*	48%*
APACHE **II** ≤16 n=56; success=51 (91%)	69%*	69%*	91%*	32%*
RBG<7mmol/l n=44; success=43 (98%)	60%*	94%*	98%*	34%*
APACHE **II** ≤16 RBG<7mmol/l N=29; success=29 (100%)	76%*	100%*	100%*	47%*
RR<30/minute APACHE **II** ≤16 N=42; success=41 (98%)	89%*	89%*	98%*	62%*
RR<30/minute RBG<7mmol/l *n=39; success=38(97%)*	79%*	92%*	97%*	55%*

The combination of baseline RR < 30 breaths per minute and random glucose < 7mmol/l increased prediction of a successful outcome from NIV to 97% while the use of all 3 factors was 100% predictive in this population.

2.5 Discussion

The data in our observational prospective cohort study supports the view that NIV is a significant advance in the management of acute decompensated hypercapnic respiratory failure complicating COPD exacerbations with over 80% of patients recovering from an episode which a decade ago would have required IPPV. This success rate is comparable to that previously reported from ICU and was not substantially different from a more mixed population of patients, many without acidosis, admitted to UK hospitals (Girault et al 2003; Price et al 2006).

In surgical and medical intensive care practice, hyperglycaemia is a known adverse prognostic marker but specific data about hyperglycaemic patients managed with NIV are limited (Christiansen et al; Umpierrez et al; Yendamuri et al; Capes et al; Baker et al). A small study suggested that 'late failure' of NIV defined by deteriorating gas exchange was more frequent in patients with an initially raised blood sugar (Moretti et al 2000). "Late failure" amounted to 31 of the 137 patients studied (22.7%). The presence of "metabolic complications" (defined as hyperglycaemia) was found to be significantly more frequent in the "late failures" i.e. hyperglycaemia was found in 7 of the "late failures" compared to 3 of the "successes" (22.5 v 3.8%). A large review of a mixed population of unselected COPD patients noted longer hospital stays and greater mortality in patients presenting with hyperglycaemia. This retrospective review examined 348 COPD exacerbations presenting to hospital over a 12 month period in 291 subjects. The mortality in the group where the blood

glucose value was > 9mmol/l was 22% which was significantly higher than the 11% mortality noted in the group where the blood glucose level was <6.0mmol/l. The risk of death was found to be increased by 10% for every 1 mmol/l increase in blood glucose. However it was not possible to adjust for the potential confounding effects of corticosteroids; the study did not distinguish between the presence and absence of ventilatory failure while many of the diagnoses based on purely clinical criteria in the absence of spirometry (Baker et al 2006). However, our study in a well-defined patient population found that hyperglycaemia, even when comparatively mild and defined at only one time point, was related to the final outcome irrespective of the diagnosis of diabetes, use of insulin or prior oral corticosteroid use. In general the degree of hyperglycaemia observed was modest but it may still reflect the significant physiological stress associated with deteriorating gas exchange and worsening lung mechanics, often accompanied by pulmonary infection. Furthermore, even modest levels of hyperglycaemia have previously been shown to be associated with significant adverse consequences in a variety of settings. In the context of patients admitted with trauma injuries, a study of 738 patients showed that a random blood glucose>7.5mmol/l was associated with a significantly higher mortality (15.5 v 2%) and this effect was even more pronounced with a blood glucose level>11.1 mmol/l (34.1 v 3.7%). Some patients had radiological evidence of pneumonia but this did not explain the occurrence of hyperglycaemia in most patients nor did it predict NIV failure. Thus, in our data initial hyperglycaemia had independent prognostic value.

Initial observational data suggested a relationship between the severity of acidosis and the outcome of AHRF in COPD, a finding supported by subsequent randomised studies. [Plant et al 2000; Bott et al 1993; Jeffrey et al 1992]. Our mean baseline pH was <7.25 in 42% of patients but, unlike the earlier studies, treatment succeeded in over 70% of cases. However,

"real world" observational studies charting the experience and outcomes of NIV over time have found that patients with a lower arterial pH (i.e. more severe degree of respiratory acidosis) were being ventilated successfully in later cohorts (Carlucci et al 2003). A study of 208 patients treated with acute NIV over a 7 year period revealed a failure rate of 17.2% with a mean pH of 7.23 which was lower than that seen in our cohort. Furthermore, in the 2nd cohort of the study examined between 1997 and 1999, the mean pH of those who succeeded from a trial of NIV was 7.21, which was the same mean pH as those who failed NIV in an earlier cohort between 1992 and 1996. The reason behind this observation may lie in individual units gaining a greater degree of experience and confidence in NIV over time and may explain why baseline pH was a poorer discriminant in the patient population now referred for NIV. Interestingly, a meta-analysis of 15 randomised controlled trials performed on NIV in acute respiratory failure (including 8 trials in COPD patients) found that whilst NIV use led to a 13% reduction in mortality overall, admission pH was not found to significantly correlate with mortality (Peter et al 2002).

In contrast, the baseline respiratory rate was a good measure of treatment response as has been seen elsewhere (Plant et al 2000; Confalonieri et al 2005; Ambrosino Thorax 1995). Confalonieri et al prospectively charted the outcome of 1033 COPD patients treated with NIV in the acute setting in order to identify predictors of outcome. Following multivariate analysis, a baseline RR between 30–34/minute carried an OR of 1.83 for failure which increased to 2.66 for a baseline RR>35/min (Confalonieri et al 2005). Interestingly, in our data, a higher baseline respiratory rate could carry an increased risk of asynchrony of the patient with the ventilator and may also be a marker of a greater intrinsic respiratory load promoting a shortened inspiratory time and more hypercapnia (Diaz et al 1997; Appendini et al 1994). As the respiratory muscles are unloaded by the effects of NIV, respiratory rate can

fall, the associated pulmonary hyperinflation lessens along with the work of breathing and dyspnoea improves (Appendini et al 1994).

We observed a relationship between the APACHE II score and clinical outcomes, which was unsurprising as this index incorporates several variables which independently predicted outcome. The mean APACHE 2 score was significantly lower in the NIV success group compared to the NIV failures (14.63 v 19.19; $p<0.001$).

Multivariate logistic regression analysis identified three factors which explained almost all the variance in outcome in our patient group and which were largely independent of each other. Receiver-operator curve analysis defined threshold values in this population, which agreed with the conventional level of elevated blood glucose in the case of hyperglycaemia and which independently identified a respiratory rate of 30, the same value used in the highly discriminant CURB65 score for pneumonia severity. The relative simplicity with which these variables can be measured suggests that a simple prognostic index can be developed based on these factors if our findings are validated in other trials. The presence of RR< 30 combined with normoglycaemia prior to the initiation of NIV carried a specificity of 92% in predicting success from NIV with a sensitivity of 79%. When baseline RR <30 was combined with normoglycaemia and APACHE II index ≤16, the specificity increased to 100%. In essence, the combination of these "favourable" criteria in a COPD patient with decompensated ventilatory failure prior to initiation of NIV predicts a successful outcome. On the other hand, in terms of predicting failure of NIV, the presence of a RR≥ 30 coupled with hyperglycaemia carried a negative predictive value of 97% and a sensitivity of 92% (the failure rate was 55% in this sub-group). We therefore conclude that the presence of these "unfavourable" criteria in a patient at baseline does not imply NIV will definitely fail but such patients may require

more intensive and aggressive monitoring as there is a significantly higher risk of treatment failure in such circumstances.

Our study has some limitations. Although being a prospective study, we recorded only one blood glucose value and this may vary during an acute illness. However, the use of a threshold value close to the upper limit of normal had significant discriminatory power when used as a binary outcome for NIV success. Furthermore, the timing of the measurement was similar in all cases i.e. upon presentation to hospital but prior to NIV initiation. In addition, the overall sample size of the study was small despite being a relatively homogenous population. A small sample size as seen in this study could potentially limit the usefulness of multivariate analysis where a significant number of candidate variables exist. It would have been of interest to determine whether COPD patients with a co-existing diagnosis of Diabetes Mellitus would ultimately carry a worse prognosis but the small sample size overall limited further investigation in this area and further larger studies are needed in this field. Our study took place in a single centre and therefore further large multi-centred studies are required examining the prognostic value of the baseline markers noted here (i.e. Respiratory rate; glycaemia and APACHE 2 score) with an emphasis on validation before our findings can be extrapolated in a more generalised fashion. We had limited information about the role of infection in these patients but again the predictive variables selected are indirectly linked to the consequences of infection. In our cohort, acute NIV carried a relatively low failure rate of 18%. This may reflect the patient selection criteria used i.e. only COPD patients receiving NIV within 24 hours of hospital admission were included. Patients developing decompensated ventilatory failure after a longer hospitalisation or when complicated by a hospital acquired infection likely represent a sicker group carrying a higher failure rate. Our failure to identify an association with baseline pH may reflect this focused entry criteria,

although the absolute values are rather lower than in several other series. The high mortality in patients who failed NIV may reflect both the severity of the initial presentation and also current UK practice towards additional supportive ventilation which continues to be a topic for debate (Wildman et al 2003). Our data relate to the first episode on an admission when the patient was ventilated and to the outcome of that episode. One individual who recovered from such an episode subsequently died before discharge but overall our mortality is in keeping with other recent reports in the literature (Carlucci et al 2003; Chu et al 2004). Although not all patients had spirometrically confirmed COPD the predictive value of hyperglycaemia remained even after excluding those cases where spirometry was not performed. Certain factors known to affect tolerance to NIV were not measured such as the degree of mask leak, the presence of secretions and the ability to remove them. The presence of glycaemia and that of a markedly elevated Respiratory Rate at baseline are reflective of the severity of the insult received by the patient but only partly determine the outcome from NIV. The success of NIV in a given patient is also dependent on variables related to the application and administration of NIV e.g. tolerance of the ventilator, level of leak, secretions etc. and our study did not accurately assess the contribution of these factors to outcome. Further research in these important areas is needed.

2.6 Summary and future directions for further study

When COPD patients develop decompensated ventilatory failure, a baseline hyperglycaemia identifies those with the greatest risk of failure with non-invasive ventilation as does an elevated respiratory rate and increased APACHE II index on admission. Combining these approaches should provide clinicians with a relatively simple way of stratifying risk at the bedside and adjusting management accordingly. Validation of this model in terms of predicting outcome from NIV in acute decompensated ventilatory failure is required in a 2nd

cohort of patients. The message emerging from this and other studies listed in Chapters 1 and 2 involving severely ill patients with a variety of presentations is that hyperglycaemia, particularly in the absence of a prior diagnosis of diabetes mellitus, is associated with a worse outcome in the critically ill. Furthermore, such studies justify further research aiming to test the utility of incorporating hyperglycaemia into "illness severity" scoring systems and whether this offers additional prognostic value aiding risk stratification.

The data from our study also support the emerging hypothesis that the outcome of COPD patients presenting with an acute exacerbation even in the absence of ventilatory failure is in fact shaped by non-respiratory variables such as cardiovascular and metabolic limitation (Seneff et al 1995). This data and the significant short and long term mortality associated with acute COPD exacerbations documented in the literature further underlines the importance of the hunt to find suitable "biomarkers" in COPD exacerbations which may help clinicians risk stratify and manage patients accordingly with other candidate variables including Troponin and Brain Natriuretic Peptide (BNP) (Koutsokera et al 2012).

We hypothesise that the hyperglycaemia observed in our study in the context of acute NIV represents a marker of significant physiological stress on the patient in the context of acute critical illness (Mizrock et al 1995). The concern was whether the poor outcomes observed in patients with hyperglycaemia were not just associative could be in part be causative i.e. secondary to hyperglycaemia-induced cellular damage (Van den Berghe et al 2004) and if those outcomes could be changed through achievement of normoglycaemia by insulin therapy. So called "tight glycaemic control" in the critically ill has had its advocates in the literature (Malmberg et al 1999; Van den Berghe et al 2001; Van den Berghe NEJM 2006). In an early study recruiting 1548 "surgical" patients to a single ITU, 765 were randomised to

"intensive insulin treatment" and 783 to "conventional treatment". Insulin was administered in the "intensive group" through continuous infusion through a central venous line using a syringe driver. The mortality in ITU was significantly less in the "intensive insulin treatment" group compared to the "conventional treatment" group (4.6 v 8.0%; p=0.04). The insulin group also showed a 46% reduction in the incidence of septicaemia as well as those needing dialysis for acute kidney injury and also impacted significantly on length of stay in ITU in the subgroup of patients needing ITU admission for 5 or more days in total (Van den Berghe 2001). These findings provoked a further multicentre study conducted by the same group where 1200 "medical" patients admitted to the ITU for were randomised to "intensive insulin treatment" or "conventional treatment" (Van den Berghe 2006). The aim of "intensive insulin treatment" was the maintenance of normoglycemia (between 4.4 and 6.1 mmol/l) whereas the "conventional treatment" arm aimed for blood glucose values ≥11mmol/l. There were no significant differences in terms of hospital mortality (37.3 v 40%) or ITU mortality (24.2% v 26.8%) between the "intensive insulin treatment" and "conventional treatment" groups. Interestingly, and perhaps relevant to our own study population, the "intensive insulin treatment" group showed quicker weaning from mechanical ventilation in those patients admitted to the ITU for ≥3 days. Furthermore, the principal reason for ITU admission was a "Respiratory diagnosis" in 49% and 51% of the "intensive insulin treatment" and "conventional treatment" respectively. When taking the subgroup of patients (n=767) who were in the ITU for ≥3 days, a significantly reduced in=hospital mortality was noted (52.5 to 43%) in the "intensive insulin treatment" group. However, subsequent data have since challenged the benefits of "tight glycaemic control" in critically ill patients (Brunkhorst et al 2008; NICE-SUGAR Study Investigators 2009). In a larger study of 6104 patients admitted to the ITU (the NICE-SUGAR study), 3054 were randomised to undergo "intensive" control and 3050 to "conventional" control. Here, "intensive" control targeted those patients where

the glucose level was ≥8 mmol aiming to achieve a target value of <6 mmol/l. This approach differed from the earlier studies where the "intensive" control only targeted those where the glucose level was ≥10 mmol/l (Van den Berghe et al 2006). Significantly in the NICE-SUGAR study, more patients in the "intensive" arm succumbed to severe hypoglycaemia (defined as blood glucose ≤ 2.2mmol/l) compared to the conventional arm (6.8% v 0.5%; $p<0.001$), a finding much more apparent compared to the earlier studies. Furthermore, achievement of normoglycaemia did not appear to impart a reduction in morbidity or length of stay in the NICE-SUGAR study; in fact 27.5% of the "intensive" arm died on the ITU compared to 24.9% of the "conventional" arm ($p=0.02$) and most were cardiovascular in nature. However, when comparing the deaths which occurred in the NICE-SUGAR study compared to the earlier multicentred study by Van den Berghe et al (2006), care was withdrawn after a median of 6 days in the former compared to 14 days in the latter which could explain the disparity in deaths observed between the 2 papers. In patients receiving NIV in AHRF complicating COPD, despite some of the "favourable" studies listed above, whether altering blood glucose levels to achieve normoglycaemia results in improved clinical outcomes or increases adverse events remains to be seen. We presently advise caution for those adopting such an approach in this area.

Chapter 3: A study of patient attitudes in the United Kingdom towards ventilatory support in COPD

3.1 Introduction

Non Invasive Ventilation (NIV) is both an effective and established therapy for COPD in this situation reducing the need for intubation and mortality while data from the literature serves to challenge some commonly held misconceptions about the value of Invasive Positive Pressure Ventilation (IPPV) in COPD regarding "ventilator dependency" and a uniformly poor outcome from such therapy (Lightowler et al 2003; Breen et al 2002; Nevins et al 2001; Seneff et al 1995). The decision to institute either of these treatment approaches must take account the patient's wishes which can be difficult to determine when he or she is extremely ill. One way around this is to actively address end of life issues when the patient is clinically stable (Chakrabarti et al 2005; Sullivan et al 1996; Gaber et al 2004). There is a paucity of data about patient attitudes towards ventilatory support in COPD. What data is available suggests that the majority of patients feel that end-of-life issues should be discussed on a routine basis (Gaber et al 2004; Curtis et al 2004; Knauft et al 2005). In addition, there is a little data regarding the role and uptake of advanced directives of care in COPD patients in the UK contrary to that seen in the USA (Heffner et al 1997; Llovera et al 1999).

In this study, the aim was to understand how various aids that may be used by healthcare professionals to discuss the issue of ventilatory support and end of life care with COPD patients' impact on the patient's perception of such interventions. Moreover, we wished to determine if an association exists in COPD between commonly measured variables such as health status, pulmonary function and capacity to perform ADLs with the willingness of such patients to receive ventilatory support during exacerbations. Such findings may give further

insight into the "thinking" behind the decision making of COPD patients regarding end of life issues. Despite the increasing availability of ventilatory support in clinical practice, patients may not always wish to receive such interventions and consequently issue an advanced directive of care. This study also aims to gain some understanding of attitudes towards the use of advanced directives of care (ADC) in UK COPD patients.

3.2 Methodology

3.2.1 Subjects

Patients with a known diagnosis of COPD who had been hospitalised during the previous 12 months due to an exacerbation were invited to participate. All were clinically stable with no exacerbations in the 6 weeks preceding the study visit. COPD and the term "exacerbation of COPD" were diagnosed according to standard criteria (Rabe et al 2007; Burge et al 2003). Exclusion criteria comprised known respiratory, cardiac, renal, gastrointestinal or neurological co-morbidity, as well as those patients being investigated for, with a current diagnosis or previous history of neoplasia. In addition, patients who had previously received NIV during an acute exacerbation of COPD or who were using domiciliary NIV were also excluded. Formal ethical approval for the study was obtained from the local Ethics Committee.

3.2.2 Study design and protocol

A 5-stage process was developed in order to explore patient attitudes towards ventilatory support by means of a structured interview. This process was designed by a focus group of Respiratory Physicians at University Hospital Aintree (RMA, CJW, LD & MIS) including the Unit Clinical Leads in COPD, NIV and Palliative Care in Respiratory Disease in consultation

with a senior Respiratory Physiotherapist. The structured questionnaire was tested in a pilot study which we have previously reported (*Sulaiman MI, Chakrabarti B, Warburton CJ, et al. A study of patient attitudes towards non-invasive ventilatory support and relation to health status in COPD. Thorax 2004;59 (Suppl II):S97*). After refinement, a standardised structured interview was conducted; these were carried out by one investigator (B.C) not involved in developing the study protocol. The interviewer was a respiratory physician experienced in managing COPD patients in the acute setting including initiation and establishment of patients on Ventilatory support. All interviews were carried out in a private location involving only the patient and interviewer at all times. The interviewer handwrote the patient responses.

3.2.3 The decision aid devised for the study

The scenario of acute decompensated ventilatory failure complicating a COPD exacerbation was first described to each patient along with the role of Ventilatory Support (both NIV and IPPV) in such situations. The interviewer described a scenario (a standardised version) to each subject where the subject was admitted to hospital with a "flare up" of the chest and where conventional medical management was failing e.g. treatment with oxygen, nebulisers and steroids etc. The situation was described as potentially life threatening and could end in death. Subjects were then introduced to the concept of a treatment which could be helpful in this scenario.

Stages 1 to 3 deal with the area of NIV whilst stages 4 and 5 approach the issue of IMV during a COPD exacerbation if NIV was unsuccessful.

Stage 1: Standardized verbal description of NIV focusing on its role in treatment of a COPD exacerbation complicated by decompensated ventilatory failure

Stage 2: Visual aid: Patient shown a photograph of an NIV machine in use on a COPD patient in the acute setting

Stage 3: Demonstration of NIV: A trial of non invasive ventilation lasting for a minimum period of 10 minutes with each subject attached to a full facemask connected to a portable non invasive ventilator (BiPaP Harmony S/T Respironics©; Ventilator settings: IPAP 10; EPAP 4; Ti:Te 1:3; Back up rate 8-12bpm) set up by the interviewer. Initially the mask is applied to the patient without the mask being strapped to the head and the patient is allowed to hold the mask for several minutes in order to gain familiarity and ease with the equipment. Following this, the mask is strapped to the patient's head for the remainder of the trial if the patient is willing and comfortable

Following each of the above stages, subjects were assessed on several aspects of the effects of that stage. They were asked how the stage had affected their willingness to receive NIV if offered during an acute exacerbation complicated by decompensated ventilatory failure; response choices being "more willing", "less willing" or "unchanged". In addition they were asked whether the stage had made them change their views from their opinion prior to that stage, and finally whether they thought the stage was useful in making a decision. At each stage, subjects were given an explanation regarding the purpose of ventilatory support during acute exacerbations of COPD whilst opportunity was given for discussion and interaction with the interviewer as well as clarification of any points the patient felt unsure with throughout the interview process.

Stage 4: A standardized detailed verbal description of the role of IPPV (along with information regarding potential adverse effects and success rates) during a COPD

exacerbation complicated by acute decompensated ventilatory failure where NIV had been unsuccessful.

Stage 5: Description of potential alternative treatments to IPPV (i.e. symptom control and palliation) during a COPD exacerbation complicated by acute decompensated ventilatory failure and where NIV has been unsuccessful.

Following stage 4 the subject's were asked about their willingness to receive IPPV if offered during an acute exacerbation in the above context. The response choices were "yes", "no" or "not sure". After stage 5, subjects were asked how the description of potential alternatives to IPPV had affected their willingness to undergo IPPV with response choices being "more willing", "less willing" or "unchanged".

Each subject was then given a standardized verbal explanation of an ADC. Subsequent to this description, each patient was asked whether they had heard of ADCs, if they had ever made one and finally, if they would be interested in making one in the future following an explanation of the process.

3.2.4 Assessment of Quality Of Life, Body Mass Index, Lung Function and Social History

Health status, symptoms, performance status and capacity to perform ADLs were assessed by means of 5 validated tools:

- St George's Respiratory Questionnaire (SGRQ) (Jones PW et al 1991)
- Medical Research Council (MRC) scale (Bestall JC et al Thorax 1999)
- Hospital Anxiety and Depression (HAD) scale (Zigmond et al 1983)
- World Health Organisation Performance Status scale

- Nottingham Extended Activities of Daily Living index (EADL) (Nouri FM et al Clin Rehabil 1987)

The EADL index (EADLi) assesses 4 areas of daily living, namely mobility, in the kitchen, domestic tasks and leisure activities by means of 21 questions; maximum EADL score attainable is 21 with lower scores indicating greater levels of disability (EADL score <16 denotes significant disability).

Each patient underwent spirometry and Body Mass Index (BMI) measurement during the same visit (Celli et al 2004).

Details of social circumstances, current medications including use of domiciliary oxygen therapy and occupational history were also recorded.

3.2.5 Statistical analysis

Statistical analysis was performed using the SPSS© software package following consultation from a medical statistician. Uni-variate analysis was performed using the Chi-squared ($\chi 2$) test in the case of categorical variables which were not linked and with linear-by-linear analysis in the case of linked categorical data. The two-tailed Mann Whitney U test was used to analyse continuous data in the absence of a normal distribution. Fisher's Exact Test was employed when dealing with groups containing comparatively fewer subjects. Spearman's Rank Correlation was used to measure the association between independently related and continuous variables while Kappa (κ) co-efficient statistics were used for categorical variables. Statistical significance was defined as a p value < 0.05.

3.3 Results

3.3.1 Baseline Demographics

61 consecutive patients meeting the inclusion criteria were contacted over a 5 month period. Of these, 50 agreed to participate in the study. The demographics of the study population are outlined in Table 1.

Table 1: Demographics of study population

Age	69 years (IQR 14 years)
Gender	34=Male (68%)
FEV1	Median 36% predicted; 0.92 litres (IQR 21%; 0.47 litres)
FVC	Median 75% predicted; 2.80 litres (IQR 26% 0.95 litres)
Oxygen use	10=LTOT (20%)
	6=Oxygen cylinder PRN use
	34=None
Social Status	15=Live alone
	35=Live with family member/spouse
	0=Residential Care/Nursing home
BMI	BMI<21=9 (18%)
	BMI≥21=41 (82%)
ADL index	18 (IQR 8)
SGRQtot	67.05 Units (IQR 26.28)
SGRQsymp	69.45 Units (IQR 49.50)
SGRQact	86.12 Units (IQR 21.43)
SGRQimp	54.45 Units (IQR 25.73)
MRC index	≥4: 33 (66%)
	3: 13 (26%)
	2: 4 (8%)

All subjects were white Caucasian and were under specialist respiratory care. FEV1 was ≤50% predicted in 86% (43/50). 3 patients had previously received IPPV during an acute exacerbation and 58% (29/50) had completed a 6 week pulmonary rehabilitation programme

in the preceding 12 months. Only one patient completed education beyond basic school level i.e. 16 years old.

3.3.2 Patient attitudes towards and willingness to receive Non-Invasive Ventilatory Support

24% (12/50) felt that the visual aid (stage 2) had been helpful in terms of making a decision whether to receive NIV. 86% (43/50) found that the demonstration of NIV (Stage 3) had been a helpful aid in decision making regarding NIV. The difference between stages 2 and 3 on whether patients perceived them to help decision making was highly significant (χ^2 test; $p<0.001$). Following stage 1 (verbal description), 96% (48/50) stated a willingness to receive NIV if offered in the acute setting. Following stage 2 (subject shown photograph of NIV in use), only 76% (38/50) stating that they would be willing to receive NIV after being shown the visual aid. Following stage 3 (demonstration) 84% (42/50) of the cohort stated that they would be willing to receive NIV. Following stage 3, 76% (38/50) stated that demonstration of NIV had increased willingness to receive it. 12% (6/50) felt less willing to receive NIV after the demonstration. These changes translated into 7 subjects who had been unwilling to receive NIV after Stage 2 now being willing to receive it and 3 subjects who had been willing to receive NIV after Stage 2 now stating that they were unwilling.

3.3.3 Patient attitudes towards and willingness to receive Invasive Ventilatory Support

Following stage 4 (detailed explanation of IMV), 60% (30/50) stated that they would be willing to receive IMV during an acute exacerbation, 30% (15/50) were unwilling to receive IMV and 10% (5/50) felt unsure regarding IMV. Overall, after stage 5 (explanation of alternative treatments to IMV including palliation and likely death), 58% (29/50) stated that

they would be willing to receive IMV 34% (17/50) were unwilling while 8% (4/50) felt unsure. Of the 3 patients who had previously received IMV, 2 stated that they would be willing to receive this again during an acute exacerbation if offered. Following stage 5, 70% (35/50) felt that their willingness to receive IMV was unchanged with 24% (12/50) feeling that they would be less willing to receive IMV and 6% (3/50) feeling more willing to receive IMV. However, during stage 5, only 2 patients actually changed their decision from stage 4 regarding whether to receive IMV (one patient who had been willing to receive IMV and one who had been unsure regarding IMV following stage 4 said that they would be now unwilling to receive IMV after stage 5). None of the group who had initially stated they would be unwilling to receive IMV after stage 4 changed their decision to being willing following stage 5.

3.3.4 Analysis of the association between willingness to receive Ventilatory Support and Clinical Variables

a) Non Invasive Ventilation

Health status (SGRQ score for all domains), EADL index, BMI, FEV1 and HADS score (both for anxiety & depression) were not associated with willingness to receive NIV following completion of stage 3 of the study (Mann Whitney U Test; $p>0.1$). In addition, willingness to receive NIV was not significantly associated with gender, domiciliary oxygen use, prior participation in a pulmonary rehabilitation programme, social status, whether currently smoking, MRC index or WHO performance status ($\chi 2$ test; $p>0.1$).

b) Invasive Ventilation

On uni-variate analysis (Table 2), willingness to receive IMV was associated with younger age and a decreased EADL score (signifying greater capacity to perform ADLs).

Table 2: Willingness to receive Invasive Mechanical Ventilation (IMV) and relationship to clinical variables (n=46) †

	Willing to receive IMV *(n=29)*	**Unwilling to receive IMV** *(n=17)*	**P value**
Age	67 years (IQR 10)	76 years (IQR 11)	0.016
Gender	Male=20 Female=9	Male=12 Female=5	0.733
FEV1 (% predicted; litres)	37%; 0.95 litres (IQR 0.49l ; 20% pred)	36%; 0.85 litres (IQR 0.56l ; 27% pred)	0.432
FVC (% predicted; litres)	80%; 2.84 litres (IQR 0.95l ; 26% pred)	74%; 2.5 litres (IQR 0.95l ; 25% pred)	0.316
Domiciliary oxygen use	None=22 PRN=3 LTOT=4	None=10 PRN=3 LTOT=4	0.393
BMI	BMI>21=24 BMI≤21=5	BMI>21=13 BMI≤21=4	0.382
EADL score	Median=20 (IQR 6)	Median=15 (IQR 7)	0.03
Social circumstances	10=Live alone 19=Live with family member/spouse 0=Residential Care/Nursing home	5=Live alone 12=Live with family member/spouse 0=Residential Care/Nursing home	0.209
MRC index	2=2 3=9 4=16 5=2	2=2 3=3 4=4 5=8	0.095 (linear)

The presence of significant disability (EADL score <16) was noted in 38% (19/50).

A significant relationship between EADL index and willingness to receive IMV was noted (χ^2 test; p=0.043, Table 3).

Table 3: the association of functional status with willingness to undergo Invasive Mechanical Ventilation (IMV)

	Not willing to undergo IMV	Not sure regarding IMV	Willing to undergo IMV
ADL less than 16 (significant disability) *N=19*	9 (47%)	3 (16%)	7 (37%)
ADL equal or greater than 16 *N=31*	8 (26%)	1 (3%)	22 (71%)

EADL index was found to be inversely correlated with SGRQ score (-0.73; p<0.001), HADS score (-0.48; p<0.001) and MRC score (-0.61; p<0.001) but no significant correlations were noted between age (-0.21; p=0.15) or FEV1 % predicted (0.23; p=0.11).

3.3.5 Patient attitudes towards Advanced Directives of Care

Prior to participating in the study, 34% (17/50) had heard of the concept of advanced directives of care though none of the group had ever issued an ADC. 48% (24/50) of the sample expressed an interest to issue an ADC having been given an explanation of the

process. No statistical significant relationship was seen between expressing an interest in issuing ADCs and any of the variables studied. (χ^2 test; $p>0.1$).

3.4 Discussion

3.4.1 The impact of aids to facilitate decision making regarding preferences for life sustaining therapy in COPD

The 2008 UK Department of Health *End of Life Care Strategy* mentions, specifically citing COPD patients as an example, that End of Life discussions should be tailored according to the individual wishes of the patient and such discussions should ideally be conducted outside the setting of an acute illness *(Department of Health. End of life care strategy: promoting high quality care for all adults at the end of life. Department of Health)*. In clinical practice, decisions regarding acute ventilatory support in COPD are usually made during the exacerbation itself leaving little time for formulation of a plan by patients, carers and health-care professionals (Knauft et al 2005; McNeely et al 1997; Travaline et al 1995; Pfeifer et al 2003). The UK End of Life Strategy cited the possible role of material for patients to read in advance of any End of Life discussion in order to aid the process of decision making *(Department of Health. End of life care strategy: promoting high quality care for all adults at the end of life. Department of Health)*. Little is known specifically regarding the impact of aids used in an outpatient setting to facilitate this decision making process for COPD patients. Dales et al developed and tested a structured decision aid in 20 patients with severe COPD comprising an information leaflet and an audio aid (Dales et al 1999). The decision aid gave patients a comprehensive overview of what is meant by IPPV describing risks and benefits in the context of an acute exacerbation and alternatives to IPPV i.e. palliation and symptom

control. Prior to receiving the decision aid, 50% chose not to receive IPPV and this increased to 60% following using the decision aid. Furthermore, when asked again 12 months later, only 2 patients had changed their decision. Only 16% of the sample stated that they had discussed this issue with their physicians beforehand, a figure which is in keeping with other studies. Furthermore, a subset of the group (n=7) agreed for their relatives to be interviewed in order to assess congruence in decision making between patients and their carer i.e. would the carer be able to guess whether the patient would wish for IPPV? Interestingly, in all 7 cases, the family member's choices were in conflict with what the patient would want. However, a criticism of this and other earlier such studies were that they were conducted prior to the emergence and widespread use of NIV during acute COPD exacerbations and thus captured a sequence of events which did not reflect current practice in the majority of cases managed today i.e. proceeding straight to IPPV without a trial of NIV beforehand. In a UK based study, leaflets explaining concepts of COPD, IPPV and NIV were used to facilitate surveys conducted by nursing staff however the impact of these was not directly assessed (Gaber et al 2004).

To our knowledge, the effect of using picture aids and comparison of this with a demonstration of NIV on decision-making regarding ventilatory support has never been studied before in a COPD population. In our study, less than a quarter of patients felt that the photograph had actually been helpful in aiding decision making whereas 86% felt that the demonstration had facilitated decision making with most subjects more willing to receive NIV. Supplying patients with a limited degree of information i.e. verbal description resulted in the greatest uptake for NIV whilst a visual aid resulted in a 22% overall fall in the number willing to undergo NIV. The experience of mask ventilation however had a positive effect with over 80% stating that the demonstration had made them more likely to receive NIV and that they would be willing to receive NIV. This compares favourably to results seen in one

other UK study where 76% of patients stated willingness to receive NIV but here only a verbal description was given (Gaber et al 2004). Our data suggest that patients would find both explanation and demonstration useful. These findings are likely to have significant implications for patient information documents and for the formulation of tools by which healthcare professionals discuss the concepts of ventilatory support and end of life issues with COPD patients when seen in the "stable state". Research incorporating both qualitative and quantitative methodologies is essential in order to explore patients' wishes in this difficult area and to identify the barriers to communication regarding end of life issues in COPD (Knauft et al 2005). Further studies are also needed to understand whether patient awareness of and familiarity with NIV when stable would lead to improved tolerance of NIV when acutely unwell and whether this would translate into improved clinical outcomes.

3.4.2 Variables associated with willingness to receive ventilatory support

Ultimately 58% of subjects stated that they would wish to receive IPPV in our study comparing favourably to other similar cohorts (Gaber et al 2004; Pfeifer et al 2003; Stapleton et al 2005). However, a novel finding from our study is that preservation of functional status, as measured by the NEADL index, was associated with increased willingness to undergo IPPV. To our knowledge, no previous study has used an ADL scale measuring functional status in regards to patient attitudes towards ventilation. Only 37% of patients with an NEADL index indicative of significant disability were willing to undergo IPPV as compared to 71% of those without significant disability. The presence of poor functional status in a patient (defined as being barely capable of getting out of bed) was a discouraging factor in 84% of physicians deciding on suitability for IPPV according to a Canadian study of COPD patients in addition to co-morbidity and advanced dementia but the views of patients were not collected by the authors (McNeely et al 1997). In that study, underlying depression and

whether the patient was still smoking were not regarded by physicians as factors that should influence the decision making of health care professionals regarding whether to administer IPPV. In our cohort, the presence of significant anxiety, depression or impaired lung function was not associated with patient willingness to receive IPPV, a finding also noted by others (Gaber et al 2004; Stapleton et al 2005).

We and other authors have observed no relationship between willingness receive life - sustaining therapy and patient's perception of health status and health related quality of life when using existing validated instruments. In a US study of 101 patients with severe COPD, 62% of patients reported that they would wish for mechanical ventilation yet no association was observed between health status as measured using St George's Respiratory Questionnaire (SGRQ) score as well as FEV1 and gender with preferences for IPPV and the same associations were noted in our own cohort (Stapleton et al 2005). Furthermore the authors reported that the presence of significant depression did not predict willingness to undergo IPPV which is similar to our own findings but here, depression was associated with reluctance to undergo cardiopulmonary resuscitation (Stapleton et al 2005). In a UK based study, 100 patients with COPD were interviewed by Respiratory Specialist Nurses who also provided patients with leaflets regarding the role of NIV and IPPV (Gaber et al 2004). In this study, health status was measured using the validated breathing problem-based quality-of-life questionnaire (BP-QoL). Again, no association was found between preference for either form of Ventilatory modality and health status.

In our study, advancing age was significantly associated with reluctance to undergo IPPV (76 years v 67 years), a finding also noted by others (Gaber et al Palliative Med 2004; Stapleton et al 2005). In the study by Stapleton et al, when taking only those patients over 65 years old, 44% preferred not to receive IPPV or CPR (Stapleton et al 2005). Interestingly, in a study exploring patient attitudes towards CPR in those aged 60 years or above in a mixed study

population, the proportion opting for CPR fell from 41% to 22% after learning of the probability of survival to discharge (Murphy et al 2004). In a previous study assessing functional status in oxygen dependent COPD patients, NEADL scores were found to correlate with HADS scores for depression, health status and FEV1 but as was also noted in our study, no correlation was found between NEADL index and age (Okubadejo et al 1997). With an increasing elderly population who suffer from chronic lung disease, the findings of this study reinforces the message that age cannot, in isolation, be used as a surrogate marker of functional limitation when considering COPD patients for life sustaining therapy.

3.4.3 Advanced Directives of Care in COPD: Barriers to End of Life discussion and Advanced Directive uptake

The Department of Health End of Life Strategy states that "Advance Care Planning" is a helpful way of eliciting patients' preferences regarding the type of care they would wish to receive and furthermore mentions that this could be achieved by the completion of a statement of the person's wishes and preferences regarding future care or an advance decision to refuse specific treatment (*Department of Health. End of life care strategy: promoting high quality care for all adults at the end of life; Department of Health).* Despite these recommendations, our study conducted in a UK population found that awareness and uptake of ADCs was low among patients with COPD and this would appear to be consistent with the findings of a recent survey of Respiratory Intermediate Care Units in Europe (Nava et al 2007). Nava et al in a Europe wide Respiratory ITU survey reported that of 6008 patients admitted to ITU, only 29.5% had any discussions about end of life decision making prior to hospital admission. However, the population studied comprised a large proportion of patients with neuromuscular conditions as well as COPD which may account for the higher uptake of ADCs compared to our cohort. In an American questionnaire based study surveying 2

pulmonary rehabilitation programmes comprising 105 COPD patients, whilst 94% of patients expressed opinions regarding preferences for mechanical ventilation, only 42% had completed an ADC (Heffner et al 1996). The explanation behind such a low uptake of ADCs is, we suspect, multifactorial in nature. The lack of uptake of ADCs may be explained by the educational background of the population being studied as only 1 subject continued education beyond 16 years of age. A US study of 115 patients identified several barriers for patients to discuss End of Life issues with healthcare professionals (Knauft et al 2005). Physicians felt hesitant in discussing such issues due to the fear of removing hope and optimism from patients, feeling that patients were not "ready" to have such discussions and the lack of time available for consultations of this nature. Interestingly, 37% of patients reported being unsure as to what life sustaining treatments they would wish for whilst the most common "patient-centred" barrier was a need to focus on staying alive rather than talking about death. A UK study of 39 health care professionals from a variety of disciplines in both primary and secondary care participated in focus group discussion which then underwent thematic analysis (Gott et al 2009). A number of barriers to End of Life Discussion and ADC uptake were described. Participants felt that often, COPD patients were given a lack of information regarding their diagnosis, clinical course and prognosis by health care professionals hence resulting in patients and carers not being prepared for episodes of deterioration requiring escalation of care. A lack of consensus as to who would be responsible e.g. General Practitioners, practice nurses, secondary care etc. for commencing such discussions was also raised with an agreement that conducting such discussions in the outpatients department when patients were clinically stable seemed to be the best scenario. Furthermore, healthcare professionals reported difficulty to determining at what stage in the condition such End of Life discussions should be initiated due to the uncertain clinical course of COPD as opposed to lung cancer. The latter theme was also described in longitudinal qualitative study of 21

COPD patients along with their professional and personal carers (Pinnock et al 2011). Whilst professional carers recognised that the condition was progressing, they expressed difficulty in identifying the time point for the transition to "palliative care" and here, again, comparisons with Lung Cancer in terms of predicting the trajectory of death were made. The authors recommended that certain "milestones" in the progression of COPD should act as a trigger for linking supportive and palliative care such as initiation of Long Term Oxygen Therapy (LTOT) or hospital admission with an exacerbation. For our study, an inclusion criteria for entry was hospitalization with an acute exacerbation in the preceding 12 months and furthermore, following a hospital admission with AHRF secondary to COPD requiring NIV, a study by Chu et al found that 49% had died within 1 year post discharge and thus, hospital admission requiring acute NIV may represent exactly such a milestone for initiating such discussions (Chu et al 2004).

Our study reported that there were no variables such as disease severity or functional limitation which predicted willingness to frame an ADC. Only a few studies have addressed this issue with relevance to COPD. Nevertheless, our data is consistent with the findings of Pfeifer et al who studied 100 patients with chronic lung disease (over half diagnosed with COPD) and evaluated the desire to discuss End of Life issues (Pfeifer MP et al 2003). The authors found that neither the severity nor impact of the disease when taking lung function, functional status, whether they had been ventilated previously or number of hospital admissions were predictive of patient receptiveness to discuss End of Life issues. Despite the lack of awareness regarding the concept of ADCs, 48% of our sample stated that they would be interested in issuing an ADC after been given an explanation of the process. This is consistent with the findings of a US study where the use of pamphlets and videotapes significantly increased uptake of ADCs (Brown et al 1999. Further research on this

potentially important subject is urgently needed including whether pulmonary rehabilitation programmes should be used as a focal point for incorporating discussions regarding End of Life issues and ADCs for COPD patients as ultimately such a model has been shown not only to increase uptake of ADCs but to a positive impact on patient perceptions of the quality of care they receive (Heffner et al 1997). However, there also remains a debate regarding the stability of ADCs in clinical practice with studies showing that patients may change their wishes after making an ADC and further studies are needed to determine whether such a phenomenon occurs in COPD patients who issue an ADC (Emanuel et al 1994; Danis et al 1991; Hardin et al 2004)

3.4.4 Limitations to the study

Our study has limitations. These observations relate to COPD patients perception when clinically stable and decision-making may differ during an acute exacerbation. The choices made by our patients regarding ventilation may have been influenced by the manner in which information was presented to them, a finding noted by other authors (Sullivan et al Chest 1996; McNeely et al 1997).

It would have been of interest to observe whether a visual aid comprising a patient receiving IPPV in the acute situation would have altered patient willingness to receive this therapy as was the case with NIV. The NEADL index was initially designed for use in patients disabled by stroke, and has subsequently been adopted for use in patients with chronic airflow obstruction (Nouri et al 1987; Okubadejo et al 1997; Dyer et al 2002; Jones et al 2005) A key limitation to its use in COPD patients is that some of the activities whilst difficult in musculoskeletal disability are easy to perform in COPD (such as feeding themselves and reading newspapers) (Connolly MJ et al 1996). The conclusions of our study may also have been limited by the relatively small sample size and furthermore, the conclusions regarding

NIV when used in the context of our study cannot be extrapolated to other applications of NIV in acute settings e.g. as a palliative tool to relieve dyspnoea and use in patients with end stage malignancies (Cuomo et al 2004)

3.4.5 Summary of study findings

Demonstration of NIV in the stable state was thought by patients to be a useful tool in facilitating decision-making regarding this form of treatment in contrast to photographic aids. Worsening functional status as measured by the NEADL index and advanced age were associated with reduced willingness to receive invasive ventilatory support in COPD patients. Advancing age did not necessarily correlate with worsening functional limitation. Awareness of the concept of Advanced Directives of Care was found to be low among COPD patients in our study although almost half of the patients expressed interest in the uptake of an Advanced Directive of Care after a full explanation of the process. Neither disease severity nor functional limitation was predictive of patient willingness to frame an Advanced Directive of Care.

Chapter 4: Airflow Obstruction in a rural Indian population: A study of aetiology, risk factors and relationship to Body Mass Index

4.1 Introduction

The global burden of respiratory disease is felt particularly in developing countries. Furthermore, in rural populations living in countries, access to adequate healthcare resources may be limited (Murray et al 1997; Patil et al 2002). Respiratory symptoms in peoples residing in India have been detailed in epidemiological studies although there remains a relative paucity of data concerning rural regions of West Bengal, a large state in Eastern India (Jindal et al 2006; Joshi et al 1975; Bhattacharyya et al 1975). Moreover, studies in India mapping the prevalence of COPD often base the diagnosis of airflow obstruction (AFO) solely on questionnaire data charting symptoms but without recording spirometry (Jindal et al 2006).There remains a need to study respiratory symptoms and define lung function in peoples residing in rural Indian settings as this has previously not been well described in such arenas. Furthermore, it would be useful to define population based predictors of airflow obstruction in a rural Indian setting where clinicians may lack access to lung function testing.

There is a growing body of literature in India exploring the impact of biomass fuels and tobacco smoking on the development of abnormal lung function and airflow obstruction (Behera et al 1991; 100; Behera et al 1994; Ray et al 1993; Bano et al 2011). Studies conducted in predominantly urban Indian settings have highlighted a relationship between low Body Mass Index (BMI), tobacco consumption, and airflow obstruction (Shukla et al 2002). Data from urban populations in India have shown reduced FEV1 to correlate positively with low BMI (Vibhuti et al 2007).These studies contrast to findings in industrialised developed countries, where the rising incidence of obesity has been linked to

the development of respiratory disease (McClean et al 2008; Crummy et al 2008). We investigated our hypothesis that being significantly underweight, a finding commonly seen in less affluent rural populations of developing countries, could be linked to the finding of airflow obstruction.

4.2 Methodology

4.2.1 Study population and protocol

All patients greater than 35 years old attending the primary care outpatient clinic (Moitri Swasthya Kendra) in Chengail, West Bengal, India were invited to participate in the study over a 12 month period commencing February 2009. This was an adult clinic based in a rural hospital that dealt with "unselected" cases irrespective of the underlying specialty.

After obtaining informed consent, subjects underwent the following:

• Completion of a structured questionnaire (See table 1). Patients completed questionnaires with the assistance of one investigator in all cases. The questionnaire was developed by a focus group comprising of a General physician based at the Moitri Swasthya Kendra clinic (PG) and Consultant Respiratory physicians based at University Hospital Aintree , Liverpool, UK (BC, PMAC, CJW) and Birmingham Heartlands Hospital, UK (RM). The questionnaire was then translated from English into the language local to the area of India in which the study was conducted (Bengali) by 2 investigators (RM & PG), this version being used for the study. Bidis were defined as hand rolled cigarettes comprising tobacco wrapped with the temburni plant.

•Measurement of body weight, height and the calculation of body mass index. Underweight was defined as BMI<18.5 kg/m^2 according to the World Health Organization reference document (World Health Organ Tech Rep Ser. 1995)

•Measurement of spirometry (conducted by one investigator) using a portable spirometer (Laptop Medikro© Kuopio, Finland) using validated criteria (Miller et al 2005). The investigator, an ancillary health worker affiliated to Moitri Swasthya Kendra, participated in 2 training workshops focusing on performing Spirometry. The ancillary healthcare worker had no prior experience in performing spirometry but assisted a General Physician on a weekly basis at the primary care clinic. Each workshop, conducted by 2 Consultant Respiratory Physicians (BC and RM), lasted 3 hours. The training included theoretical and practical aspects of spirometry, diagnosis of AFO according to GOLD criterion and an assessment to ensure that the health care worker could perform spirometry independently (Rabe et al 2007).Calibration of the spirometer was performed daily during the study period.

The spirometry data were independently analysed by a Respiratory Clinical Physiologist (VM) blinded to the questionnaire results and graded into 3 categories:

1. Good quality: Explosive start on flow-volume curve producing acceptable Peak Expiratory Flow (PEF); met end of test criteria of <25mls exhaled in 1 second; back extrapolation volume <150mls/5% of FVC; FVC duration ≥ 6 seconds; no coughs, leaks or extra breaths. Reproducibility criteria could not be assessed as only the best manoeuvre was available on the spirometry report.

2. Adequate shape of the expiratory curve: Explosive start on flow-volume curve; back extrapolation volume <150mls/5% of FVC; no coughs, leaks or extra breaths, allowing accurate and valid estimation of FEV1.

3. Poor quality: All other spirometry that failed to meet criteria for groups 1 or 2.

Only those data in categories 1 and 2 were deemed acceptable for further analysis and further categorised as "Acceptable" spirometry. AFO was defined as an FEV1/FVC ratio < 0.7.

Cases of "Acceptable" spirometry exhibiting AFO were stratified according to severity using GOLD criteria as "normal" values for the local population have not been established (European Community for Coal and Steel).

Formal ethical approval to conduct the study was granted by the Board of the Moitri Swasthya Kendra Hospital.

Table 3: Questionnaire used for the study

Occupation: current:
previous
Smoker (Current/Ex/never): what smoked?
No of years you have been smoking?
Have you ever been diagnosed or treated for tuberculosis?
Did you have chest trouble when you were young?
Do you cook with a stove indoors?
Do you usually have a cough or have you ever had a cough in the last 12 months?
Have you ever had an attack of wheezing or tightness in your chest during the last 12 months?

Do you usually bring up phlegm from your chest first thing in the morning?
Do you usually bring up phlegm from your chest at any time of the day?
Do you feel breathless on walking at your own pace on the level?
Do you feel breathless on walking fast on the level or climbing up a slight hill?
How often is your sleep disturbed by cough, breathlessness, chest tightness or wheezing?

4.2.2 Statistical analysis

Analysis was performed using SPSS 18.0. Data are presented as mean and standard deviation (SD) unless otherwise stated. Predicted values for lung function were based on the European Coal and Steel Community (ECSC) reference values (European Community for Coal and Steel. 1983).

Statistical significance was defined as a p value <0.05. Chi squared testing was used to examine differences between categorical variables. ANOVA analysis was used to compare the mean of normally distributed variables between two groups. Spearman's Rank Coefficient was used to measure correlation between two sets of data. Logistic regression analysis was used to identify candidate variables associated with the presence of airflow obstruction.

4.3 Results

4.3.1 Baseline demographics

During the study period, 416 patients attending the clinic consented and were recruited to the study and all successfully completed the questionnaire. None were excluded from the analysis at this point. 111 patients with adequate spirometry were deemed to be of "good quality" (category 1), the shape was deemed to be "satisfactory" in a further 175 (category 2), hence 286 spirometry traces (69% of the overall sample) were categorised as "Acceptable" i.e. suitable for analysis of FEV1. These 286 subjects who had complete questionnaire data and valid spirometry were used in the analysis (see table 2 for key demographics of study population).

Table 4: Demographics of study population

Age (Median)	50 (Range 35) years		
BMI	21.38 (4.08)		
Smoking Status	Never smoked	178 (62%)	
	Ex-smoker	46 (16%) ex	
	Current smoker	62 (22%) current	35 (56%) bidis only 2 (3%) cigarettes only 25 (41%) bidis and cigarettes

Sex	Male	135 (47%) male	33/135 (24%) never smokers
	Female	151 (53%) female	145/151 (96%) never smokers
Occupation	Housewife	140 (49%) (0% male; 1 (0.7%) current/previous smoker)	
	Jute worker	26 (9%) (96% male; 21 (81%) current previous smoker)	
	Farm labourer	60 (21%) (95% male; 34 (73%) current/previous smoker)	
	Other	60 (21%) (88% male; 42 (70%) current/previous smoker)	
History of childhood chest complaints	Yes	18 (6%)	
	No	268 (94%)	
History of treatment for Tuberculosis	Yes	26 (9%)	
	No	260 (91%)	

All but 2 subjects in employment had "blue collar" occupations. All 140 subjects in the "housewife" occupation category cooked with an indoor stove, the cooking fuel being Liquid Petroleum Gas (LPG) distributed by government subsidy.

4.3.2 Relationship between respiratory symptoms and lung function

47 (16%) of all subjects were noted to exhibit AFO (GOLD "mild" stage 1 in 7 (15%); GOLD "moderate" stage 2 in 23 (49%); 12 GOLD "severe" stage 3 (26%); 5 GOLD "very severe" stage 4 (10%). The incidence of AFO was significantly higher in males (22% (30/105)) than in females (11% (17/151) Chi squared analysis, p=0.01). None of these subjects had a known respiratory diagnosis.

24% (15) of current smokers and 26% (12) ex-smokers were found to exhibit AFO on spirometry compared to 11% (20) of never smokers (Chi squared test; p=0.006). Thus, never smokers comprised 43% (20/47) of all AFO cases. The percentage predicted values of FEV1 and FEV1/FVC were significantly lower in current and ex-smokers compared to never smokers (see Table 3).

Table 5: Relationship between smoking status and lung function

	Current smoker N=62	Ex-smoker N=46	Never smoker N=178	P value (ANOVA)
FEV1 (litres) %predicted	2.19 (0.68) 71.85 (20.43)	2.14 (0.79) 71.52 (19.51)	1.85 (0.63) 79.80 (21.60)	 P=0.008

FVC (litres) %predicted	2.93 (0.71) 77.87 (16.60)	2.76 (0.88) 74.96 (17.57)	2.25 (0.76) 81.27 (21.10)	 P=0.117 (NS)
FEV1/FVC ratio	0.73 (0.12)	0.75 (0.11)	0.83 (0.11)	P<0.001

The presence of cough, wheeze, morning phlegm, phlegm at any time of day and breathlessness on the level was significantly higher in subjects with AFO (see table 4).

Table 6: Respiratory symptoms in relation to airflow obstruction on spirometry

Symptom (%/number of subjects)	All subjects (n=286)	Subjects with airflow obstruction (n=47)	Subjects without airflow obstruction (n=239)	P value (Chi squared test)
Cough	62 (177)	79 (37)	59 (140)	0.006
Wheeze	52 (148)	62 (29)	30 (71)	<0.005
Morning phlegm	29 (83)	45 (21)	26 (62)	0.003
Phlegm at any time of the day	43 (122)	55 (26)	40 (96)	0.042

Breathlessness on flat	52 (149)	70 (33)	49 (116)	0.009
Breathlessness on gradient	79 (226)	87 (41)	77 (185)	0.30

29% (52/178) of never smokers reported the presence of wheeze compared to 44% (21/45) and 45% (28/62) of ex and current smokers (ANOVA; p=0.027).

44% (27/62) of current and 33% (15/46) of ex-smokers reported presence of morning phlegm compared with 23% (41/178) of never smokers (ANOVA; p=0007).

No significant differences were noted between the never, ex and current smokers in terms of reporting breathlessness either on a gradient (78 v 87 v 79%) or on the level (50 v 53 v 57%).

4.3.3 Factors associated with the development of airflow obstruction

On logistic regression analysis, factors associated with the development of AFO were:

1. Increasing age (95% CI 0.004-0.011; p=<0.005)
2. Smoking status: Those "current" or "ex-smokers" (95% CI 0.07-0.174; p=0.006)
3. Male gender (95% CI 0.19-0.47; p=0.012)
4. Reduced BMI (95% CI 0.19-0.65; p=0.02)
5. Occupation: Those not belonging to the "housewife" category (95% CI 0.12-0.84; p=0.08)

A history of childhood chest complaints, use of an indoor stove when cooking or a known history of prior treated TB was not associated with AFO.

4.3.4 Relationship between occupation, symptoms and lung function

21% of housewives reported the presence of morning phlegm which rose to 30% in farm labourers, 35% in cotton/jute workers and 43% in "other" occupations (Mean square=13.68; F=9.24; p=0.003). There were no other significant differences in respiratory symptoms between the occupational groups. A significant relationship was noted between occupation and airflow obstruction on spirometry; an FEV1/FVC ratio<0.7 was found in 11% (15/140) of housewives compared with 18% (11/60) of "Other occupations", 22% (13/60) of farm labourers and 31% (8/26) of cotton/jute workers and (p=0.035).

4.3.5 Relationship between BMI, respiratory symptoms and lung function

23% (66/286) of subjects were classified as being "underweight" i.e. BMI<18.5 kg/m^2. The mean BMI was significantly lower in the 47 patients with AFO diagnosed on spirometry (20.11 (SD 4.02) v 21.62 (SD 4.01) kg/m^2; p=0.02). Those "current smokers" were found to have a significantly lower BMI compared to "never smokers" (19.36 (SD 3.46) v 22.35(SD 4.12) kg/m^2; p<0.001) and males were found to have a significantly lower BMI when compared with females (20.03 (SD 3.51) v 22.59 (SD 4.19) kg/m^2; p<0.001). The mean BMI in those male "current smokers" (n=60; 19.29 (SD 3.46) kg/m^2) was significantly lower than those male "never smokers" (n=33; 21.15 (SD 3.38) kg/m^2 p<0.001).

A significant association was observed between BMI and AFO on spirometry (Coefficient= -0.137; p=0.02) percentage predicted FEV1 (Coefficient= 0.14; p=0.02), FVC (Coefficient=0.13; p=0.03) and Peak Expiratory flow (Coefficient=0.14; p=0.02) with a non-significant trend noted between BMI and FEF 25-75% (Coefficient=0.1; p=0.09). Of the 286

subjects, 23% (66) were noted to have a BMI<18.5 kg/m^2 with AFO being observed in 27% (18/66) of such cases falling to 13% (29/220) of subjects with a BMI ≥18.5 kg/m^2 (p=0.013).

4.4 Discussion

4.4.1 The relationship between BMI and airflow obstruction

This study showed that within a rural Indian population, tobacco-smoking, advanced age and male gender were factors linked with an increased incidence of airflow obstruction which is in keeping with those conducted in Western industrialised settings. However, in this population, the BMI was found to be <18.5 kg/m^2 in 23% of subjects reflecting a higher proportion of underweight subjects compared to studies conducted in Western populations. A survey of adults in Mumbai found a strong relationship between tobacco consumption and a low BMI, seen particularly in bidi smokers although spirometry was not performed in this study (Pednekar et al 2006). A BMI<18.5 kg/m^2 was found to be twice as prevalent in bidi smokers. 32% of male bidi smokers had a BMI <18.5 kg/m^2 compared to 13.5% of "never smoking" males in this study and the authors suggested that tobacco use, particularly bidis, represented an independent risk factor for low BMI. These findings are comparable to the data presented here where the mean BMI was significantly lower in "current smokers" when compared to "never smokers" with 97% of current tobacco users smoking bidis. However, this study expands further on this hypothesis suggesting that being underweight in a rural Indian population is associated with the finding of airflow obstruction on spirometry as well as tobacco smoking. The mean BMI was significantly lower in subjects with airflow obstruction in this study with the incidence of airflow obstruction doubling in those with a BMI below 18.5 kg/m^2. The association between a markedly low BMI and the finding of airflow obstruction has been described previously. Interestingly, a study of 12, 576 non-

smoking individuals followed up over 26 years revealed that those with the lowest BMI carried the highest risk of developing "respiratory disease" during the latter years of follow up although the findings did not allow differentiation between specific diagnoses such as COPD. (Lindsted et al 1998). In a Belgian study of steelworkers, a correlation was observed between low BMI and obstructive spirometry in current smokers (Nemery et al 1983). However, in this study, the BMI in the "current smokers" group was 26.84 kg/m^2 compared to 28.26 kg/m^2 in non-smokers, substantially higher values than those seen in our group reflecting the two entirely different populations studied. Perhaps more relevant to the data presented here, in a study of 202 COPD patients and 136 controls from New Delhi, FEV1 was found to positively correlate with a low BMI (Vibhuti et al 2007). However, the mean BMI in the COPD population was 21.7 kg/m^2, again higher than in this study suggesting that "underweight" was less relevant within this urban Indian population compared to a rural one as seen in the population studied here. Low body weight has been shown to correlate with degree of emphysema seen on Computerised Tomography in COPD patients and has been implicated as a predictor of the development of COPD in longitudinal studies (Renvall et al 2009; Higgins et al 1982). Such data suggest a mechanistic relationship between low body weight, smoking tobacco and loss of lung function leading to the development of AFO.

4.4.2 The prevalence of respiratory symptoms in a rural Indian population and role of occupational exposures in the development of abnormal lung function

Comparatively little is known regarding respiratory symptoms within rural populations of developing countries such as India. The population studied in this paper displayed a high prevalence of respiratory symptoms. Just over 50% reported breathlessness while walking on the flat and this increased to 79% when reporting breathlessness on a gradient. 62% reported the presence of cough with 29% reporting production of phlegm in the morning. A report of 2400 rural households in the neighbouring state of Orissa found that one third of males had

symptoms of a cough in the preceding 30 days. 12% and 10% of males and females were classified as having airflow obstruction by spirometry with half of all males displaying a BMI<19 kg/m^2. (Duflo et al 2008(43): 71-78). A study of 486 farmers in 7 villages in Northern India found that 21% reported respiratory symptoms with a higher prevalence in non-smokers (Behera Lung India 2005).

Globally, the population attributable risk for COPD as a result of occupational exposures has been estimated to be 19%-20% in the overall population and rises to 31% in "never smokers" (Boschetto et al 2006, 1:11; Balmes et al 2003). Particularly relevant in the present study population, the deleterious effects of jute and cotton exposure on the respiratory system are well documented (Zuskin et al 1994;66(1):43-48; Chattopadhyay et al 2003). A 5 year follow up study of 50 workers in a Chinese jute factory found a significant reduction in FEV1 compared to matched controls that were not exposed to jute or any other dusts (Liu et al 1992). Here, the mean decline in FEV1 was 90mls compared to just 32mls on controls. Regarding the effects of cotton, a cohort of 773 cotton yarn manufacturers were followed up with lung function testing over a 3 year period. The authors reported that this group exhibited an annual decline in FEV1 of 16 mls per 100 cubic microgram average cotton dust exposure which was significantly higher when compared with a control group who worked in synthetic mills (Glindmeyer et al 1991). A 15 year longitudinal cohort study of 447 cotton textile workers in Shanghai China reported that 62% reported dyspnoea, 75% chronic cough and 73% reported symptoms of chronic bronchitis over the study period (Christiani et al 2001). The authors found that the annual decline in FEV1 was 32mls in the group overall and 43.7% in smokers. The findings from our paper are comparable to what has been described in the literature previously. In comparison to cotton/jute workers and farm labourers, housewives had a significantly lower prevalence of airflow obstruction (31% v 11% respectively) whilst

35% of cotton/jute workers reported the presence of morning phlegm production compared to 21% of housewives.

4.4.3 The relationship between indoor stove use and the finding of airflow obstruction

Contrary to previous reports from the Indian literature, the use of an indoor stove was not associated with an increased risk of having airflow obstruction in the study population described in this paper. One reason for this may be because the chief cooking fuel used by our population was liquid petroleum gas (LPG) rather than biomass fuel with users of the latter historically exhibiting an increased prevalence of respiratory symptoms and abnormal lung function (Dutt et al 1996). Dutt et al compared 3 groups each consisting of 105 women cooking with biomass, kerosene and LPG using questionnaire data capturing respiratory symptoms as well as measuring lung function. 23% of the biomass group reported respiratory symptoms compared with 8% of the LPG group ($p<0.01$). The authors reported that both FEV1 and FVC were also found to be significantly lower in the Biomass group ($p<0.01$). In another Indian study of 3071 women (of which 3068 were non-smokers) who cooked with a household domestic stove,12.6% of those using biomass fuels complained of respiratory symptoms compared to just 9.9% of those using Liquid Petroleum Gas (LPG) (Behera et al 1991). LPG was exclusively used by subjects in our study as cooking fuel. A study of 369 randomly selected subjects from a village in Western India and conducted a 2 stage process consisting of questionnaire survey and pulmonary function testing (Saha et al 2005). 90% of the 204 females studied reported using only biomass as a cooking fuel whilst only 8% used LPG as the sole cooking fuel. All subjects had consistently used the fuel described for the previous 10 years with a mean cooking time of 2-3 hours daily. The percentage predicted FEV1 was significantly higher in the "LPG" group when compared with the "biomass" arm (93.15% v 86.90%; $p<0.01$). However, the authors did not attempt to correlate the lung function with any respiratory symptoms reported by the cohort. Outside India, similar

conclusions have also been reached in studies comparing LPG with Biomass fuel highlighting a decreased incidence of COPD in subjects using the former (Ekici et al 2005). Hence, the findings emerging from this study and the others described above appear to reaffirm the beneficial effects on Lung Health gained from providing rural households subsidised LPG gas as a cooking fuel rather than the continued use of biomass.

4.4.4 The finding of airflow obstruction in never smokers

This present study found that 43% of all cases of airflow obstruction were seen in never smokers. Whilst this may represent a relatively high proportion in the cohort, the concept of COPD being a condition afflicting non-smokers is not a new one and this data is in keeping with previous reports from the literature. In a UK based cohort of 8215 individuals undergoing spirometry, 8.7% of "never smokers" were diagnosed with COPD and 29.5% of the 1093 COPD cases were seen in "never smokers" (Shahab et al 2006). Data from the US Third National Health and Nutrition Examination Survey revealed that "never smokers" comprised 23% of all airflow obstruction cases with those authors reporting low BMI as a factor associated with airflow obstruction in addition to male gender, a history of allergy and increasing age (Celli et al Am J Med 2005). The BOLD study cohort reported that "never smokers" made up 27.7% of all COPD cases; "never smokers" with moderate to severe COPD tended to be older, displayed less educational attainment, reported more frequent exposure to an indoor open cooking fire with coal and being exposed to organic dusts in the workplace (Lamprecht et al 2011). In Latin America, the PLATINO study assessed the prevalence of COPD in 5 countries and found that the proportion of those COPD cases that were "never smokers" ranged from17% in Venezuela to 31.8% in Chile (Menezes et al 2005). The multi centred IBERPOC study assessing COPD prevalence in Spain reported that 23% of COPD cases were observed in non-smokers (Pena et al 2000). Interestingly, in the IBERPOC data, females comprised 76.3% of the overall "non-smoking" cohort. However, perhaps more

relevant to our own dataset, the issue of non-smoking females developing COPD was highlighted by a study performed in South India where 900 non-smoking females from rural households were randomly selected and underwent respiratory symptom assessment and measurement of lung function according to standard criteria (Johnson et al 2011). COPD was diagnosed in 2.44% of subjects. The use of biomass fuels carried an OR of 1.44 for COPD following logistic regression and other significant variables were advancing age, use of an indoor stove and a greater duration of cooking. The concept of "non-smoking" females being at risk of developing COPD as described in the studies above is at odds with the perception of COPD in Western Industrialised nations where such a group would be regarded as being relatively low risk in this respect.

4.4.5 Limitations of this study

This study has limitations. Subjects were drawn from a population attending a clinic treating patients with "unselected" medical problems making extrapolation difficult in a general Indian population. In this present study, the lung function technician received training and reinforcement in performing spirometry from Respiratory Consultants which may not be possible in all rural areas of India. The use of the GOLD definition for AFO has been controversial with opponents arguing that this will lead to over diagnosis of AFO in the elderly (Calverley et al 2004; Hardie et al 2002). However, the difficulty in using proposed alternative definitions in defining AFO i.e. lower limit of normal lies in that the normal values and prediction equations defined for Caucasian populations may not always reflect those seen in rural Indian settings (Aggarwal et al 2005). The data presented in this study did not assess atopic status, IgE level or bronchodilator reversibility so it was not possible to accurately distinguish asthma from COPD and it is conceivable that a proportion of the cases

of AFO in our sample represented cases of asthma particularly in the cohort of "never smokers." It would have been useful in a larger sample to correlate symptoms that may be characteristic of asthma in our study e.g. nocturnal cough, wheeze with evidence of airflow obstruction on lung function testing. Furthermore, it was not possible to quantify the effect of parasitic diseases such as "tropical pulmonary eosinophilia" which may also cause symptoms such as breathlessness, cough and wheeze. Importantly, our results and analysis did not distinguish the important confounder of tobacco smoking in those subjects with a low body mass index or those who carry the relevant occupational exposures deemed to carry an increased risk of exhibiting airflow obstruction. For example, a far higher proportion of those subjects who were jute workers and labourers were tobacco smokers compared to the population who were housewives, the latter were almost exclusively non-smokers. Our results showed a higher prevalence of airflow obstruction in those who were jute workers and labourers but separating the contribution of tobacco smoke from occupational exposure to the finding of airflow obstruction in a given individual was not done. Further research involving larger studies with robust statistical analysis are required to separate the confounding effect of tobacco smoke exposure in such populations if we are to truly understand the aetiology of COPD in the developing world. In addition, it would have been useful to have analysed the group of "ex smokers" regarding risk factors and the contribution of occupational exposures but this would have required a larger sample size.

4.4.6 Summary and future directions for further study

This study demonstrates that in a rural Indian setting, airflow obstruction was related to advancing age, a history of current or previous smoking, male gender, occupation and a reduced BMI.

In rural Indian settings, our findings suggest that clinicians should maintain a high index of suspicion to consider the presence of airflow obstruction in underweight individuals, particularly when being underweight exists in conjunction with the other risk factors described. Whilst a BMI of 21 kg/m^2 or less has been shown to represent an adverse prognostic indicator in the multi-dimensional "BODE" index, additional study is required to determine whether indicators such as the BODE index would be as informative within rural Indian populations diagnosed with COPD where the risk factors for developing COPD may differ to that seen in Western Industrialised nations (Celli et al 2004). Such longitudinal studies should aim to determine whether modifying those risk factors identified with the development of airflow obstruction in rural developing world settings e.g. such as being underweight or reduction in the use of biomass would lead to a decrease in the overall prevalence of COPD and severity of airflow obstruction observed in the population studied. In view of the larger proportion of patients being significantly underweight in our cohort, further studies are also needed within rural Indian settings exploring the role of nutritional factors particularly in utero and during early life and any link they may have to the development of COPD in later years as well as assessing the impact of nutritional interventions in both the prevention of respiratory disease as well as the effects on outcome of those who have already been diagnosed with COPD.

Chapter 5: Final Conclusions from this thesis and Suggestions for Future Research

This thesis illustrates the burden of COPD in the developed and developing world as well as highlighting future research avenues in both settings. In the developed world, exacerbations of COPD represent a significant burden of hospital admissions in the United Kingdom and carry appreciable in-hospital mortality (Roberts et al 2011). Respiratory acidosis and decompensated ventilatory failure has been shown to complicate 20% of exacerbations needing hospitalization and the mortality from such episodes is reported to stand at 25% (Roberts et al 2011). Hyperglycaemia has been shown to convey an adverse prognostic outcome in COPD exacerbations but whether this holds true for patients receiving Non Invasive Ventilation (NIV) was not previously known. The data from this thesis showed that the presence of baseline hyperglycaemia increased the risk of failure of NIV in such a setting. The presence of a baseline Respiratory Rate less than 30 breaths per minute, normoglycaemia and an APACHE 2 score $\leq$16 were highly predictive of a successful outcome of NIV. Validation studies are needed to determine whether this bedside index retains its predictive power in larger prospective cohorts. On the other hand, the presence of a Respiratory Rate greater than 30 breaths per minute, hyperglycaemia and an APACHE 2 score greater than 16 at baseline has been shown to convey a worse outcome and further studies are required to determine whether adopting a more intensive policy of surveillance with greater attention to optimization of ventilation in such "high risk" patients would translate into greater survival from decompensated ventilatory failure. Furthermore, the recognition of hyperglycaemia as carrying an increased risk of treatment failure in acute ventilatory failure adds further weight to its inclusion in illness severity scales and further research is required in this area. Whilst studies assessing the impact of tight glycaemic control have yielded conflicting results to date, it is not known whether lowering the blood glucose in a hyperglycaemia cohort of

COPD patients receiving NIV in the acute setting will lead to improved clinical outcomes (Brunkhorst et al 2008; NICE-SUGAR Study Investigators 2009; Van den Berghe et al 2001; Van den Berghe NEJM 2006).

Whilst NIV has become a standard of care in the management of COPD patients presenting with decompensated ventilatory failure, it is recognised that Ventilation may be unsuccessful or deemed inappropriate in a proportion of cases (Roberts et al 2011). A Department of Health report relating to acute hospital End of Life care cited the particular problem area of a failure of clinicians to recognise when continuation of treatment was not in the best interests of the patient (*Department of Health. End of life care strategy: promoting high quality care for all adults at the end of life. Department of Health 2008*). Therefore discussions with patients regarding attitudes, beliefs and preferences towards Mechanical Ventilation and End of Life Care would appear to be integral to the management of severe COPD and that such discussions should ideally be conducted in the stable state rather than in the context of an acute exacerbation itself. However, despite this recommendation, previous to this study, very little UK data exists about which specific aids COPD patients may use to facilitate decision making and the awareness and uptake of Advanced Directives of Care. This study comprising 50 COPD patients undergoing a 5 stage interview process reported that both an explanation and demonstration of NIV had facilitated decision making in contrast to a picture aid. Further studies are needed to determine whether adopting such an approach in routine clinical practice results in improved patient and carer satisfaction in the "real world" scenario and whether this approach in the stable state translates into improved clinical outcomes through better tolerance and acceptance of NIV when acutely unwell. In order to complement the data gathered from this and other similar studies, further research is needed with a qualitative methodology charting the "patient experience" of acute NIV from hospital admission to discharge. Subsequently, use of the themes gained from such research could

frame the delivery of "patient information" given to individuals in the outpatient clinic who are deemed at high risk of needing NIV acutely in future. Whilst over half the sample was willing to be invasively ventilated in the context of an acute exacerbation, greater impairment of functional status when measured objectively was associated with a decreased willingness to receive Invasive Mechanical Ventilation along with advancing age. Interestingly lung function and patient's perceived health status did not predict willingness to receive invasive ventilatory support. None of the sample had ever taken an Advanced Directive of Care but nearly half were interested in doing so after having heard an explanation of this process. There remains a need to better understand the role of Advanced Directives when applied not to a "general population" but to a population of patients with severe COPD to assess why COPD patients choose to either adopt or forego the uptake of Advanced Directives. Such research should adopt in part qualitative techniques and encompass COPD patients from differing geographical regions and social strata within the United Kingdom. It would also be of interest to see whether incorporating education regarding Ventilatory Support, End of Life Care and uptake of Advanced Care Directives into Pulmonary Rehabilitation programmes translate into greater patient and carer satisfaction particularly if admitted acutely and such issues become clinically relevant. Further studies also with a qualitative methodology are needed to better understand the thinking behind those COPD patients who either wish to receive or choose to forego Ventilatory support if we are to practice in a truly reflective manner.

Taking a developing world scenario, the study described in Chapter 5 recruited adult subjects over the age of 35 from a rural general medical clinic in Eastern India and measured respiratory symptoms as well as assessing lung function via spirometry. The use of Liquid Petroleum Gas as cooking fuel was not associated with the finding of airflow obstruction in contrast to the body of literature highlighting the detrimental impact of biomass fuels on lung

health that underpins the public health benefits of introducing this intervention (Dutt et al 1996). Whilst tobacco smoking and male gender were associated with the finding of airflow obstruction, being underweight also increased the risk of having airflow obstruction on spirometry. These contrasts to findings in industrialised developed countries, where the rising incidence of obesity has been linked to the development of respiratory disease (McClean et al 2008; Crummy et al 2008). In the developing world, less is known regarding the epidemiology of COPD and how COPD develops particularly in populations residing in rural areas of countries such as India. The data presented in this thesis illustrates the relevance of being "underweight" (defined as a BMI under 18.5 kg/m^2) as a risk factor for an individual developing airflow obstruction particularly if combined with a significant additional insult such as tobacco consumption. A BMI of less than 18.5 kg/m^2 is a comparatively rare finding in the industrialised developed world but more prevalent in rural regions of developing world nations. Such data is an example of how risk factors for a condition with a label as COPD may vary from the developed to the developing world and furthermore, little is known regarding low Body Mass Index and outcome from COPD in the developing world. Further studies are needed to determine whether a low BMI serves as an adverse prognostic marker to the same degree in COPD patients residing in developing world countries as is seen in the Industrialised Western world (Celli et al 2004).

The prevalence of airflow obstruction in the study was found to be 16% in the group overall with none of the sample previously having a known respiratory diagnosis. Further research is needed to find ways to better identify those individuals with COPD in rural developing world settings with an emphasis on identifying those who are at greatest need and who would benefit most from the treatments (i.e. those with more clinically severe disease) given the paucity of resources in such regions. One area for further research lies in whether in rural India, adopting a policy of screening those individuals who possess the key risk factors

highlighted by our paper and other similar studies such as low body weight, smoking, biomass and occupational exposures. Further studies are hence required to determine whether in rural resource-poor regions of the developing world, adopting a policy of targeted "screening" of such high risk individuals leads not only to an increased early detection of COPD patients but also to an improvement in subsequent clinical outcomes. Regarding the association between low BMI and the development of airflow obstruction, some studies conducted in the developed world suggest that nutritional support may alter outcome in COPD patients (Schols et al1998). However, it remains to be seen whether modifying the BMI in underweight individuals through this and other interventions might improve the outcome in COPD populations in rural developing world settings where perhaps the effects of nutritional deficiency may be more pronounced. Furthermore, larger epidemiological studies are required to determine whether modification of the BMI may prevent the development of abnormal lung function and obstructive lung disease in susceptible individuals.

Chapter 6: References

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